SYNTHETIC STUDIES IN NITROGEN CHEMISTRY

BY

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

1992

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To My Beloved Parents

ACKNOWLEDGEMENTS

First of all, I am deeply indebted to my advisor, Professor Alan R. Katritzky, for his valuble guidance, encouragement and trust during these years, like a "strict father" to his son. It has been a rewarding experience and a pleasure to work with him.

Second, I would like to express my sincere gratitude to Drs. James A. Deyrup, Eric J. Enholm, David E. Richardson and Stephen G. Schulman for their helpful suggestions and time as my supervisory committee members.

I would like to give my special thanks to Dr. Stanislaw Rachwal for his valuable help and cooperation during these years. I would also like to thank Dr. Wei-Qiang Fan, Dr. John V. Greenhill, and many friends in this big research group who are too many to mention individually, for their friendly help.

I would like to thank Dr. Peter J. Steel for his X-ray structure determinations of my compounds.

Finally, I am deeply indebted to my parents for all their encouragement and support, without which I could not have become a doctor.

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Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy

SYNTHETIC STUDIES IN NITROGEN CHEMISTRY

BY

JING WU

May, 1992

Chairman: Alan R. Katritzky, FRS
Major Department: Chemistry

N,N-Bis(benzotriazolylmethyl)arylamines were obtained quantitatively from mixtures of benzotriazole, formaldehyde and the corresponding arylamine in refluxing toluene with azeotropic removal of water. Treatment of these adducts with Grignard reagents or sodium borohydride afforded symmetrically substituted *N,N*-dialkylarylamines in high yields. Unsymmetrically substituted *N,N*-dialkylarylamines could also be obtained by similar stepwise procedures. Sterically hindered *N,N*-bis(*sec*-butyl)arylamines were prepared by alkylations of the anions of the corresponding arylamines with 2-iodobutane.

Chlorosulfonation of 2-nitroanisole gave 4-methoxy-3-nitrobenzenesulfonyl chloride, which was converted with *N*-butyl-(3-phenylpropyl)amine into the corresponding benzenesulfonamide. Hydrolysis of the methoxy group and reduction of the nitro substituent of this benzenesulfonamide, followed by diazotization and coupling with 2-naphthol, afforded *N*-butyl-*N*-(3-phenylpropyl)-4-hydroxy-3-(2-hydroxy-1-naphthyl)azobenzenesulfonamide.

Medium-sized (7 and 8) benzosultams were synthesized by Friedel-Crafts cyclizations of ω-phenylalkanesulfamoyl chlorides, which were prepared by treatment of the corresponding amines with sulfuryl chloride.

New (benzotriazol-1-yl)methyl derivatives of type $Bt(1)CH_2X$ {Bt(1)= benzotriazol-1-yl} were prepared. Depending on reaction conditions, ethyl α-(benzotriazol-1-yl)acetate was converted to (*E*)-(benzotriazol-1-yl)formaldoxime or (benzotriazol-1-yl)formamide as the Beckmann rearrangement product of (*Z*)-(benzotriazol-1-yl)formaldoxime. Structures of both the oxime and the amide were confirmed by *X*-ray crystallography. α-(Benzotriazol-1-yl)acetophenone was converted to a number of interesting derivatives.

Lithiation of 1-methylbenzotriazole followed by treatments with electrophiles gave various α-substituted 1-methylbenzotriazoles. Other 1-(*n*-alkyl)benzotriazoles did not give stable anions, but treatments of their mixtures with alkyl halides by lithium diisopropylamide (LDA) afforded the corresponding α-alkylated products.

Simple treatments of 2-alkylbenzotriazoles by LDA gave symmetrical α,β-bis-(benzotriazol-2-yl)alkanes stereospecifically as the α,α-coupled products in high yields. A molecule $[Bt(2)CH(CH_3)CH(CH_3)CH(CH_3)CH(CH_3)Bt(2)]$ {Bt(2)= benzotriazol-2-yl} with four asymmetric centers derived from four molecules of 2-ethylbenzotriazole was obtained as a single isomer by simple treatment of 2-ethylbenzotriazole with LDA. α-Alkylation of 2-alkylbenzotriazoles could be achieved in high yields by reactive alkyl halides. 2-Methylbenzotriazole added quantitatively to benzophenone to give the corresponding tertiary alcohol but did not react with aldehydes. A new radical mechanism was first proposed to account for the chemistry of 2-alkylbenzotriazoles.

CHAPTER I
A BRIEF INTRODUCTION

In recent years, benzotriazole has been used extensively as a useful synthetic auxiliary in this research group, and many types of organic compounds, e.g., various aliphatic and aromatic amines, hydroxylamines, hydrazines, amides, aminoacids, ethers, esters, etc., have been synthesized [91T2683]. This dissertation focuses on synthetic studies of nitrogen compounds, especially benzotriazole, as well as their chemistry. Chapter II covers mainly the application of benzotriazole in preparation of both symmetric and unsymmetric *N,N*-dialkylarylamines. In Chapter III, synthesis of both acyclic and cyclic sulfonamides are discussed. In Chapter IV, some interesting chemistry of benzotriazole derivatives is discussed. Finally, lithiation of both 1-alkyl and 2-alkylbenzotriazoles are investigated in Chapter V. While the lithiation of the former gives the expected results, the results of the latter were initially quite surprising. Some very interesting new types of compounds were prepared, and a radical mechanism was first proposed to explain the experimental results.

CHAPTER II
DEVELOPMENT OF SYNTHETIC METHODOLOGY FOR TERTIARY AROMATIC AMINES

2.1 Foreword

In recent years, the application of benzotriazole in organic synthesis, as well as studies of its chemistry, has been developed extensively in our laboratory [91T2683]. In this chapter, we will demonstrate that condensation of one molecule of a primary aromatic amine and two molecules of benzotriazole and formaldehyde, respectively, followed by a Grignard reaction affords the corresponding symmetrically *N,N*-dialkylated tertiary aromatic amine. Unsymmetrically *N,N*-dialkylated amines can also be prepared by a stepwise procedure.

Preparation of sterically hindered tertiary aromatic amines, e.g., *N,N*-bis-(*sec*-alkyl)arylamines, is usually difficult (see section 2.3.1). We now report a convenient method for preparation of such sterically hindered amines by alkylation with 2-iodobutane.

2.2 *N,N*-Dialkylation of Aromatic Amines

2.2.1 Introduction

Tertiary aromatic amines are an important class of organic compound and have applications in many areas of chemistry, as well as in other scientific fields. Although there are many ways to prepare aliphatic amines and primary and secondary aromatic

amines, relatively few preparation methods for tertiary aromatic amines exist, and each of these methods has certain limitations.

Reductive alkylation of amines with aldehydes and ketones is one of the classical methods for preparation of amines, but the emphasis is on aliphatic amines rather than aromatic amines. Dialkylation of primary aromatic amines with ketones to form tertiary aromatic amines is extremely difficult, and that with aldehydes is less difficult, but formation of tertiary amines is dependent on the structure and reactivity of the aldehyde [B-71MI].

Direct alkylation of amines with alkyl halides is another conventional method for the preparation of amines. However, with certain alkyl halides, such as sterically hindered halides and those which are liable to eliminations under basic conditions, dialkylation of a primary amine will be difficult.

Tertiary aromatic amines can also be prepared by the reaction of aryl halides with alkali amides of secondary amines via benzyne intermediates [62CRV81], but very strong basic conditions are required and, for *para*-substituted aromatic halides, mixtures of *meta*- and *para*-substituted aromatic amines are obtained.

Aromatic halides activated by strong electron-withdrawing groups (e.g., the nitro group) undergo nucleophilic substitution reactions with primary and secondary amines to give the corresponding secondary and tertiary aromatic amines [87CL1187]. This reaction has limited applications because of the requirement for strong electron-withdrawing groups, and the yields for the preparation of tertiary aromatic amines are low.

In recent years, several reports have appeared regarding the *N*-alkylation of anilines with alcohols [80GEP2918023, 78MIP65766, 80NKK279, 81TL2667, 86JAP-61238768, 86MIP89025]. Most of these were transition metal catalysed reactions with

methanol or ethanol under high temperatures, and usually a mixture of mono and dialkylated anilines was obtained.

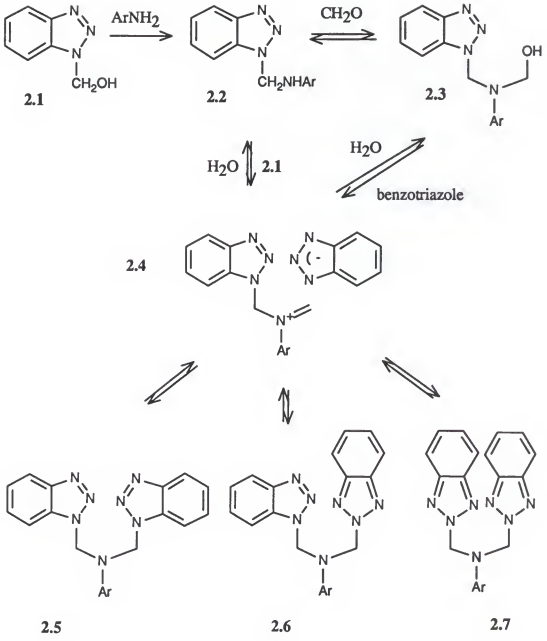
Benzotriazole as a useful synthetic auxiliary has been used extensively in recent years in our laboratory [91T2683]. *N*-Monoalkylation of arylamines can be achieved in high yield by the reaction of Grignard reagents with *N*-(benzotriazolylmethyl)-arylamines [87JCS(P1)805]. *N,N*-Dialkylated alkylamines [89JCS(P1)225], hydroxyl-amines [89JCS(P1)225] and hydrazines [89JCS(P1)2297] can also be prepared by the reactions of Grignard reagents with the corresponding *N,N*-bis(benzotriazolyl-methylated) primary aliphatic amines, hydroxylamine and hydrazines. We now report that under more vigorous conditions, *N,N*-dialkylation of primary aromatic amines can also be achieved.

2.2.2 Results and Discussion

2.2.2.1 *N,N*-Bis(benzotriazolylmethylation) of arylamines

Primary aromatic amines react rapidly with 1-hydroxymethylbenzotriazole (**2.1**) homogeneously in alcohols [76IJC(B)718, 87JCS(P1)799] or heterogeneously in water [89OPP139] to give the corresponding mono-substituted *N*-(benzotriazolylmethyl)aryl-amines. The same result is obtained by mixing benzotriazole, formaldehyde and an arylamine; instead of formaldehyde, other alkyl and aryl aldehydes can also be used [87JCS(P1)799, 89OPP139]. All these reactions proceed essentially quantitatively.

It is found from this laboratory that when equimolar amounts of 1-hydroxymethylbenzotriazole (**2.1**) and *N*-(benzotriazol-1-ylmethyl)arylamine (**2.2**) were mixed, they reacted to give an equilibrium mixture of three isomers: *N,N*-bis-(benzotriazol-1-ylmethyl)arylamine (**2.5**), *N*-(benzotriazol-1-ylmethyl)-*N*-(benzotri-azol-2-ylmethyl)arylamine (**2.6**) and *N,N*-bis(benzotriazol-2-ylmethyl)arylamine (**2.7**),


ArNH2
CH2O
CH2OH
CH2NHAr
OH
N
Ar
2.1
2.2
2.3
H2O
2.1
H2O
benzotriazole
2.4
2.5
2.6
2.7

Scheme 2.1

Table 2.1 Analytical Samples of Isomeric Mixtures of *N,N*-Bis(benzotriazolylmethyl)arylamines **2.5a-e, 2.6a-e, 2.7a-e.**

Cmpd.	Ar	Molecular Formula	Recrystallization Solvent	Cryst. Form	M.P. (°C)	Yield[a] (%)	Analysis[c] (%) C	H	N
a	4-$MeOC_6H_4$	$C_{21}H_{19}N_7O$	THF	prisms	120	55	65.7 (65.4)	5.0 (5.0)	25.7 (25.4)
b	4-$Me_2NC_6H_4$	$C_{22}H_{22}N_8$	THF	needles	163	62	66.3 (66.3)	5.6 (5.6)	28.5 (28.1)
c	4-ClC_6H_4	$C_{20}H_{16}N_7Cl$	dioxane	polyhedrons	114	73	61.7 (61.6)	4.1 (4.1)	25.3 (25.2)
d	3-ClC_6H_4	$C_{20}H_{16}N_7Cl$	THF	prisms	106	32	61.3 (61.6)	4.1 (4.1)	25.2 (25.2)
e	2-EtC_6H_4	$C_{22}H_{21}N_7$		oil	-	-		b	

a) Yield for crystalline samples; glassy mixtures of isomers **2.5-2.7a-e** were obtained in quantitative yields.
b) Rapid hydrolysis of the product in air made its analysis impossible.
c) Analyses in brackets are calculated values.

plus the unreacted starting material (**2.2**) which usually existed as a major component [90CJC446].

However, under more vigorous conditions (refluxing in toluene with removal of water) primary aromatic amines reacted with 2 moles of **2.1** to form *N,N*-bis(benzotriazolylmethyl)arylamines in quantitative yields. Use of benzotriazole, a primary aromatic amine and aqueous formaldehyde gave similar results. Alkylation of the amino nitrogen atom by **2.1** leading in the first step to **2.2** and then to **2.5**, **2.6** and **2.7** is a feasible reaction route. However, the adducts **2.3** are probably also involved as intermediates, especially when an amine, benzotriazole and aqueous formaldehyde are used directly (Scheme 2.1). The *N,N*-bis(benzotriazolylmethyl)arylamines (**2.5-2.7**) were characterized by CHN analysis (Table 2.1) and ^{1}H and ^{13}C NMR spectra (Tables 2.2-2.5).

Table 2.2 Methylene ^{1}H NMR and Composition of the Isomeric Mixtures of *N,N*-Bis(benzotriazolylmethyl)arylamines **2.5a-e**, **2.6a-e**, **2.7a-e**.

Cmpd.	Ar	Chemical Shifts				Composition (%)		
		2.5	**2.6**		**2.7**	**2.5**	**2.6**	**2.7**
a	4-$MeOC_6H_4$	6.06	6.18	6.39	6.46	65	31	4
b	4-$Me_2NC_6H_4$	6.04	6.16	6.38	6.45	66	32	2
c	4-ClC_6H_4	6.14	6.22	6.40	6.47	43	45	12
d	3-ClC_6H_4	6.18	6.26	6.44	6.50	49	46	5
e	2-EtC_6H_4	6.00	6.01	6.14	6.31	67	22	11

Note: Solutions in $CDCl_3$; chemical (δ) shifts in ppm from TMS.

The rapid equilibrium of *N*-{α-(benzotriazol-1-yl)alkyl}amines with their benzotriazol-2-yl [Bt(2)] isomers in solution is well known [75JCS(P1)1181, 87JCS(P1)2673]. As expected, we found that all three isomers **2.5**, **2.6** and **2.7** were present in solutions of the freshly prepared *N,N*-bis(benzotriazolylmethyl)anilines. In

Table 2.3 ^{1}H NMR Spectra of *N,N*-Bis(benzotriazol-1-ylmethyl)arylamines **2.5a-e**.

Cmpd.	NCH_2N (s 4H)	Benzotriazole 4 (d 2H)	Benzotriazole 5 6 7 (m 6H)	Ar ortho	Ar meta	Ar para	Substitutes
a	6.09	8.00 (8.3)	7.34	6.95 (d 9.0 2H)	6.73 (d 9.0 2H)	-	3.68 (s 3H)
b	6.00	7.98 (7.9)	7.31	6.83 (d 8.9 2H)	6.50 (d 8.9 2H)	-	2.78 (s 6H)
c	6.19	8.05 (8.3)	7.41	7.15 (d 8.0 2H)	7.23 (d 8.0 2H)	-	-
d	6.18	8.01 (8.4)	7.38	6.98 (d 7.9 1H) 7.25 (t 2.1 1H)	7.18 (t 8.2 1H)	7.10 (d 8.2 1H)	-
e	5.99	8.02 (8.3)	7.34	6.49 (d 8.0 1H)	7.15 (m 2H)	6.86 (t 7.8 2H)	0.99 (t 7.6 3H) 2.46 (q 7.6 2H)

Note: Solutions in $CDCl_3$; chemical shifts (δ) in ppm from TMS; coupling constants J (in brackets) in Hz; only the major coupling constants were considered.

Table 2.4 ^{13}C NMR Spectra of *N,N*-Bis(benzotriazol-1-ylmethyl)arylamines **2.5a-e**.

Cmpd.	CH_2	Benzotriazole						Ar				Subst.
		C(4)	C(5)	C(6)	C(7)	C(7a)	C(3a)	ipso	ortho	meta	para	
a	64.5	119.6	123.9	127.5	109.7	132.7	145.8	138.7	123.7	114.7	156.7	55.2
b	64.9	119.3	123.8	127.3	109.9	132.7	145.6	134.8	123.9	113.1	148.0	40.3
c	63.4	129.9	124.3	128.0	109.5	132.6	145.9	144.4	120.6	129.7	128.7	-
d	63.1	120.0	124.5	128.2	109.5	132.6	145.8	146.7	116.9	130.8	123.4	-
									119.1	135.6		
e	64.9	119.7	124.2	127.7	109.7	133.1	145.7	143.3	126.4	127.3	126.9	14.5
									141.0	129.6		22.8

Note: Solutions in $CDCl_3$; chemical shifts (δ) in ppm from TMS.

Table 2.5 ^{13}C NMR Spectra of *N*-(Benzotriazol-1-ylmethyl)-*N*-(benzotriazol-2-ylmethyl)arylamines **2.6a-e**.

Cmpd.	CH_2Bt(1)	CH_2Bt(2)	Bt(1)			Bt(2)		Ar				Subst.
								ipso	ortho	meta	para	
a	64.8	71.7	109.8	119.9	124.1	118.3	126.7	139.2	120.5	114.7	155.6	55.5
			127.8	132.9	146.0	144.4						
b	65.0	71.8	109.9	119.5	123.7	118.0	126.3	135.6	121.0	113.4	147.1	40.5
			127.3	132.6	145.7	144.1						
c	63.5	70.3	109.5	120.0	124.3	117.8	127.0	144.3	118.3	129.4	127.1	-
			128.1	132.9	145.9	143.9						
d	63.3	70.0	109.5	120.1	124.5	118.3	127.0	146.9	114.4	130.6	122.0	-
			128.2	133.0	145.9	144.5			116.6	135.3		
e	66.1	73.0	110.3	119.5	124.1	118.3	126.7	141.4	126.7	127.4	126.8	13.2
			127.5	133.0	145.9	144.4			141.4	129.4		23.8

Note: Solutions in $CDCl_3$; chemical shifts (δ) in ppm from TMS; Bt(1)= benzotriazol-1-yl; Bt(2)= benzotriazol-2-yl.

the ^{1}H NMR spectra, the methylene groups of these isomers appeared as easily recognizable singlets at slightly different positions; two singlets of equal intensity were observed for isomers **2.6** for the two different methylene groups. The ratios of these integrals reflected the percentages of these isomers in the isomeric mixture. Data obtained from the ^{1}H NMR spectra of the freshly prepared products (isolated by simple evaporation of the solvent) are collected in Table 2.2.

The crude oily or glassy mixtures of isomers **2.5**, **2.6** and **2.7** could often be converted into crystalline materials by trituration with diethyl ether (sometimes cooling by dry ice was required). The compositions of isomers **2.5**, **2.6** and **2.7** of these crystalline samples from trituration or recrystallization were often different from those of the initially obtained mixtures because of isomerization.

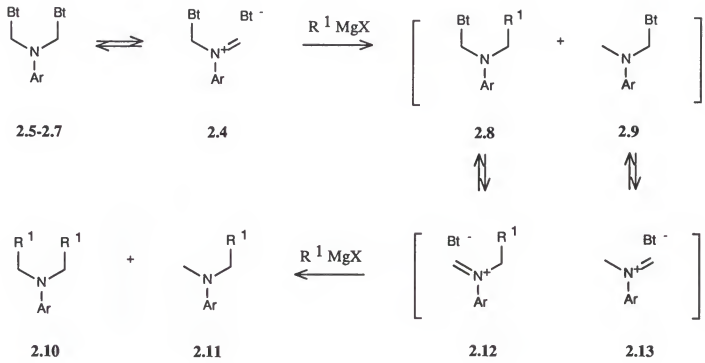
Benzotriazole moiety gives quite steady ^{1}H NMR signals, especially its ^{13}C NMR signals. Therefore, it was not difficult to make ^{1}H and ^{13}C NMR assignments for the major isomer **2.5** (Tables 2.3 and 2.4) and ^{13}C NMR for isomer **2.6** (Table 2.5).

Bis(benzotriazolylmethylation) failed for a few aromatic amines: 2- and 4-aminopyridines gave only the corresponding *N*-monosubstituted aromatic amines **2.2** under the standard conditions because of their low basicities (pKa= 2.0 and 2.3 [78JOC3123] respectively, compared to 4.05 for 4-chloroaniline [54MI726]).

2.2.2.2 Grignard reactions on *N,N*-bis(benzotriazolylmethyl)arylamines

2.2.2.2.1 Symmetric *N,N*-dialkylarylamines

Similarly to *N*-mono(benzotriazolylmethylated) arylamines [87JCS(P1)805], *N,N*-bis(benzotriazolylmethyl)arylamines **2.5**-**2.7** were easily reduced by sodium borohydride, or reacted readily with Grignard reagents to produce *N,N*-dimethyl or *N,N*-dialkylarylamines **2.10**, respectively (Scheme 2.2). The alkyl group in the product



Bt = benzotriazol-1-yl or benzotriazol-2-yl

Scheme 2.2

Table 2.6 Characterization of Amines **2.10a-g**.

Cmpd.	Ar	R^1	R^2	Molecular Formula	Grignard Reagent	Yield (%)	Picrates			
							M.P. (°)	Found (Calcd.) (%) C	H	N
a	3-ClC_6H_4	$PhCH_2$	$PhCH_2$	$C_{22}H_{22}ClN$	$PhCH_2MgCl$	56	118	59.8	4.5	9.8
								(59.5)	(4.5)	(9.9)
b	4-ClC_6H_4	i-Pr	i-Pr	$C_{14}H_{22}ClN$	i-PrMgBr	39	a	a	a	a
c	Ph	cyclohexyl	cyclohexyl	$C_{20}H_{31}N$	$C_6H_{11}MgBr$	33	86[b]	84.3[b]	11.1[b]	4.8[b]
								(84.2)	(11.0)	(4.9)
d	2-EtC_6H_4	H	H	$C_{10}H_{15}N$	$NaBH_4$	77[c]	135	50.8	4.8	14.8
								(50.8)	(4.8)	(14.8)
e	Ph	H	$PhCH_2$	$C_{15}H_{17}N$	$PhCH_2MgCl$	99	114	57.2	4.5	12.7
								(57.3)	(4.6)	(12.7)
f	Ph	CH_3	$PhCH_2$	$C_{16}H_{19}N$	$PhCH_2MgCl$	87	122	57.8	4.8	12.3
								(58.2)	(4.9)	(12.3)
g	Ph	Pr	$PhCH_2$	$C_{18}H_{23}N$	$PhCH_2MgCl$	38	oil[b]	85.3[b]	9.2[b]	5.5[b]
								(85.3)	(9.2)	(5.5)

a) Picrate did not form; HR MS calcd. for $C_{14}H_{22}NCl$: 239.1440. Found: 239.1417.

b) Data for the free amines.

c) Literature yield: 8% [65MI1437].

Table 2.7 ^{1}H NMR Spectra of Amines **2.10a-g**.

Cmpd.	Ar[a]				CH_2R^1	CH_2R^2	R^1, R^2
	ortho	meta	para	subst.			
a	6.61	7.21	6.66	-	3.41	3.41	2.78 (t 8.0 4H)
	(d 7.8 1H)	(t 7.7 1H)	(d 7.8 1H)		(t 7.9)	(t 7.9)	7.14 (t 8.0 2H)
	6.70						7.16 (d 7.0 4H)
	(t 2.0 1H)						7.29 (t 7.7 4H)
b	6.54	7.10	-	-	3.10	3.10	0.87 (d 6.7 12H)
	(d 9.0 2H)	(d 9.0 2H)			(d 7.3)	(d 7.3)	2.03 (m 2H)
c	6.61	7.19	6.65	-	3.14	3.14	0.91 (m 4H) 1.16 (m 6H)
	(d 8.1 2H)	(t 7.3 2H)	(t 7.5 1H)		(d 6.6)	(d 6.6)	1.69 (m 12H)
d	7.07	7.20	7.01	1.25	2.67	2.67	-
	(d 9.0 1H)	(d 7.5 1H)	(t 9.0 1H)	(t 7.5 3H)	(s)	(s)	
		7.16		2.73			
		(t 9.0 1H)		(q 7.4 2H)			
e	6.67-6.76	7.16-7.32	6.67-6.76	-	3.55	2.87	2.84 (t 7.5 2H)
	(m 2H)	(m 2H)	(m 1H)		(t 7.6)	(s)	7.16-7.32 (m 5H)
f	6.72	7.15-7.33	6.67	-	3.49	3.30	R^1: 1.11 (t 7.1 3H)
	(d 8.1 2H)	(m 2H)	(t 7.2 1H)		(t 7.8)	(q 7.1)	R^2: 2.86 (t 7.8 2H) 7.15-7.33 (m 5H)
g	6.66-6.73	7.17-7.33	6.66-6.73	-	3.50	3.21	R^1: 0.92 (t 7.3 3H) 1.32 (sxt 7.9 2H)
	(m 2H)	(m 2H)	(m 1H)		(t 7.6)	(t 7.5)	1.53 (qnt 8.1 2H) R^2: 2.85 (t 8.1 2H)
							7.17-7.33 (m 5H)

Note: Chemical shifts (δ) in ppm from TMS; coupling constants (in brackets) in Hz.
a) Only main coupling constants were considered.

Table 2.8 ^{13}C NMR Spectra of Amines **2.10a-g**.

Cmpd.	Ar					$CH_2(R^1)$	R^1				
	ipso	ortho	meta	para	subst.	$CH_2(R^2)$	R^2				
a	148.8	110.3	130.7	116.1	-	53.5	33.8	126.7	128.9	129.1	139.6
		112.1	135.7								
b	146.8	113.5	128.7	119.8	-	60.4	20.3	26.2			
c	148.2	112.0	129.0	114.6	-	59.2	26.0	26.6	31.3	35.8	
d	152.4	119.1	126.3	123.3	14.8	45.1	-				
		138.7	128.9		23.4						
e	148.8	112.1	129.2	116.1	-	38.4	-				
						54.7	32.9	126.1	128.5	128.8	139.8
f	147.5	111.8	129.3	115.6	-	45.0	12.3				
						52.3	33.8	126.1	128.4	128.7	139.7
g	147.7	111.7	129.3	115.5	-	50.9	14.0	20.3	29.5		
						52.9	33.5	126.1	128.5	128.7	139.7

Note: Chemical shifts (δ) in ppm from TMS.

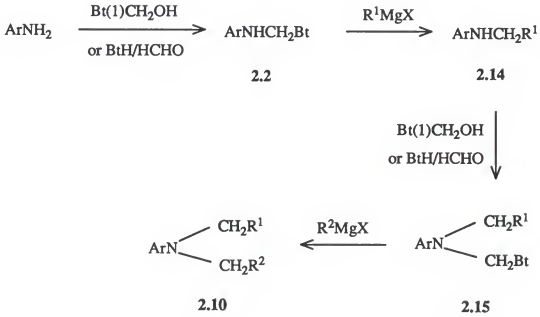
contains an extra methylene compared to that of the Grignard reagent, and this method is therefore especially valuable when the alkylating agents for direct alkylation of the amine are not easily available, or for alkylating agents which undergo elimination easily in basic conditions. Thus, *N,N*-di(2-phenylethyl)anilines (e.g., **2.10a**) were first prepared by this method.

N,N-Dialkylarylamines prepared by the present method can be generally obtained in good yields (Table 2.6). The products were fully characterized by CHN analysis and ^{1}H and ^{13}C NMR spectra (Tables 2.6, 2.8 and 2.9). This method is comparable to the published method of reaction of *N,N*-bis(phenylthiomethyl)anilines with Grignard reagents [67JOC2892], but with the advantages of the easier preparation of starting material *N,N*-bis(benzotriazolylmethyl)anilines in comparison with their phenylthiomethyl analogues, and the avoidance of dealing with harmful and unpleasant sulfur compounds.

The present method has some limitations: (1) all alkyl groups of *N,N*-dialkylarylamines are linked to the nitrogen by methylene groups, and thus limited to only primary alkyl groups; (2) protection is required for arylamines bearing substituents which are sensitive towards Grignard reagents; and (3) sometimes *N*-alkyl-*N*-methylamines **2.11** (Scheme 2.2) were obtained as side products, especially when secondary alkyl Grignard reagents [61JA3966, 42JA1239] were used.

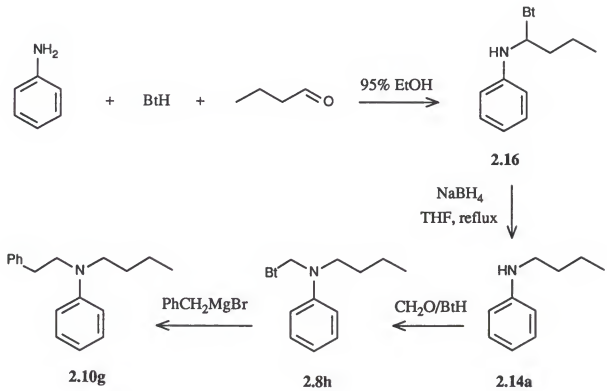
2.2.2.2.2 Unsymmetric *N,N*-dialkylarylamines

By applying a stepwise procedure, tertiary arylamines with two different alkyl groups can also be prepared as illustrated in Scheme 2.3. Condensation of primary arylamine $ArNH_2$ with one mole of 1-hydroxymethylbenzotriazole (**2.1**) gives compound **2.2**, which can be subsequently converted to the monoalkylated arylamine **2.14** upon treatment with Grignard reagent R^1MgX [87JCS(P1)799, 87JCS(P1)805].



Bt(1) = benzotriazol-1-yl

Scheme 2.3


NH2
+
BtH
+
O
95% EtOH
Bt
HN
2.16
NaBH4
THF, reflux
HN
2.14a
CH2O/BtH
Bt
N
2.8h
PhCH2MgBr
Ph
N
2.10g

Scheme 2.4

By using the same methodology on compound **2.14**, the second different alkyl group R^2 can be introduced and the unsymmetric *N,N*-dialkylamine **2.10** is obtained. Compounds **2.10**e-g were prepared by this methodology (Tables 2.6, 2.7 and 2.8).

Alternatively, the monoalkylated amine **2.14** can be prepared by reduction (sodium borohydride) of the corresponding *N*-{α-(benzotriazolyl)alkyl}arylamine, which can be easily prepared in high yield from an aldehyde, benzotriazole and an appropriate primary aromatic amine [87JCS(P1)799]. Thus compound **2.10g** was prepared by this method (Scheme 2.4).

2.2.3 Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus or with a hot-stage microscope and were not corrected. Proton and carbon NMR spectra were obtained on a Varian VXR-300 instrument in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) as the internal standard. Coupling constants (J) were given in Hz. High resolution mass spectra were recorded at 70 ev with an A.E.I. MS-30 mass spectrometer with a Kratos DS-55 data system. Elemental analyses were performed under the supervision of Mr. M. Courtney. Diethyl ether and tetrahydrofuran (THF) were dried by refluxing with sodium and benzophenone and distilled immediately prior to use. Silica gel for column chromatography was 230-400 mesh.

2.2.3.1 General procedure for the preparation of *N,N*-bis(benzotriazolylmethyl)arylamines

Benzotriazole (11.91 g, 100 mmol), an aromatic amine (50 mmol), 37% aqueous formaldehyde (11.2 ml, 150 mmol) and toluene (50 ml) were stirred at 60 °C for 1 h and refluxed with a Dean-Stark water trap for 3 h. The solvent was evaporated under reduced pressure to give the product (**2.5a-e**, **2.6a-e** and **2.7a-e**) as a glassy

substance, which was characterized by analysis and NMR (Tables 2.1-2.5). In many cases, this glassy product was transformed into a crystalline material by trituration with dry ether.

2.2.3.2 Preparation of symmetric *N,N*-dialkylarylamines

Preparation of *N,N*-bis(2-phenylethyl)-3-chloroaniline (**2.10a**). To a solution of benzylmagnesium chloride prepared from benzyl chloride (4.60 ml, 40 mmol) and magnesium turnings (1.46 g, 60 mmol) in ether (30 ml) was added a solution of *N,N*-bis(benzotriazolylmethyl)-3-chloroaniline (3.90 g, 10 mmol) in tetrahydrofuran (20 ml) and stirred for 24 h. The reaction mixture was poured into 10% ammonium chloride (100 ml) and extracted with toluene (3 x 50 ml). After washing with water (50 ml), 10% NaOH (50 ml), water (2 x 50 ml), drying (Na_2CO_3) and removal of the drying reagent and solvent, *N,N*-bis(2-phenylethyl)-3-chloroaniline (**2.10a**, 3.74 g, 56%) was obtained. Compound **2.10a** was characterized by analysis and NMR (Tables 2.6-2.8).

Preparation of 4-chloro-*N,N*-diisobutylaniline (**2.10b**). Aqueous formaldehyde (37%, 22.8 ml, 0.3 mol) was added to a solution of benzotriazole (23.83 g, 200 mmol) and *p*-chloroaniline (12.76 g, 100 mmol) in toluene (150 ml) preheated to 60 °C. After stirring for 1 h, the mixture was refluxed under a Dean-Stark water trap for 3 h and allowed to cool to 25 °C. To this solution was added isopropyl magnesium bromide prepared from isopropyl bromide (36.90 g, 300 mmol) and magnesium turnings (9.72 g, 400 mmol) in ether (150 ml). The mixture was stirred and refluxed under argon for 2 h and poured into a mixture of ice and water (200 g). The mixture was neutralized with acetic acid, extracted with ether (2 x 200 ml), washed with water (2 x 400 ml), 10% sodium hydroxide (2 x 200 ml), water (2 x 400 ml), and dried (Na_2CO_3). The drying agent and solvent were removed to give crude **2.10b** (20.35 g) as a reddish brown viscous liquid.

The crude product consisted of 4-chloro-*N*,*N*-diisobutylaniline (**2.10b**, 39% yield, the characteristic doublet of CH_2 in the ^1H NMR at δ 3.10), the starting material 4-chloro-*N*,*N*-bis(benzotriazol-1-ylmethyl)aniline (**2.5c**, 30% yield, CH_2 singlet at δ 6.18), 4-chloro-*N*-isobutylaniline (**2.14b**, 19% yield, CH_2 doublet at δ 2.88) and 4-chloro-*N*-isobutyl-*N*-methylaniline (**2.11b**, 10% yield, CH_2 doublet at δ 3.15 and CH_3 singlet at δ 2.90).

An analytical sample of 4-chloro-*N*,*N*-diisobutylaniline (**2.10b**) was obtained by column chromatography (1:1 hexane/benzene) and characterized by analysis and NMR (Tables 2.6-2.8).

Preparation of *N*,*N*-bis(cyclohexylmethyl)aniline (**2.10c**). To a stirred solution of *N*,*N*-bis(benzotriazol-1-ylmethyl)aniline (7.15 g, 20 mmol) in dry THF (20 ml) was added dropwise the Grignard reagent prepared from cyclohexyl chloride (7.11 ml, 60 mmol) and magnesium turnings (1.94 g, 5 mmol) in ether (40 ml), stirred under argon for 50 h, and poured into 20% ammonium chloride (100 ml). This mixture was extracted with toluene (100 ml), washed with water (100 ml), 10% sodium hydroxide (100 ml), water (100 ml), and dried (Na_2CO_3). Removal of the drying agent and solvent afforded a crude product (9.66 g) consisting of *N*,*N*-bis(cyclohexylmethyl)aniline (**2.10c**) and *N*-(cyclohexylmethyl)-*N*-methylaniline (**2.11c**) in a molar ratio of 3:1. Separation of a crude sample (1.47 g) by column chromatography (2:1 hexane/benzene) afforded pure **2.10c** (0.38 g), which was characterized by analysis and NMR (Tables 2.6-2.8). The second fraction gave **2.11c** (0.04 g). ^1H NMR: δ 0.86-1.02 (2 H, m), 1.12-1.30 (3 H, m), 1.62-1.81 (6 H, m), 2.94 (3 H, s), 3.11 (2 H, d, J = 6.7 Hz), 6.62-6.73 (3 H, m), 7.18-7.28 (2 H, m). ^{13}C NMR: δ 26.0, 26.6, 31.1, 36.9, 39.6, 59.7, 111.6, 115.4, 129.0, 149.5. HR MS calcd. for $C_{14}H_{21}N$: 203.1674. Found: 203.1674.

Sodium borohydride reduction of *N,N*-bis(benzotriazol-1-ylmethyl)-2-ethylaniline. Preparation of *N,N*-dimethyl-2-ethylaniline (**2.10d**). A mixture of 2-ethylaniline (6.06 g, 50 mmol), benzotriazole (11.91 g, 100 mmol), 37% aqueous formaldehyde (9.12 ml, 120 mmol) and toluene (100 ml) was stirred for 2 h at 20 °C and refluxed for 3 h with a Dean-Stark water trap. The solvent was removed to give a clear orange oil (19.44 g), which was dissolved in 1,4-dioxane (50 ml) and refluxed with sodium borohydride (1.77 g, 46.8 mmol) for 4.5 h. The reaction mixture was diluted with ether (200 ml), washed with 5% NaOH (100 ml), water (2 x 100 ml) and dried (Na_2CO_3). After removal of the drying agent and solvent, **2.10d** (5.75 g, 38.5 mmol, 77%) was obtained as a colorless liquid. The product was characterized by analysis and NMR (Tables 2.6-2.8).

2.2.3.3 Preparation of unsymmetric *N,N*-dialkylarylamines

Preparation of *N*-methyl-*N*-phenethylaniline (**2.10e**). A mixture of *N*-methylaniline (10.72g, 100 mmol), benzotriazole (11.91 g, 100 mmol), aqueous formaldehyde (37%, 9.12 ml, 120 mmol) and toluene (100 ml) was stirred for 2 h and refluxed for 3 h with a Dean-Stark water trap. The solvent was removed under reduced pressure to give a mixture (23.86 g) of *N*-(benzotriazol-1-ylmethyl)-*N*-methylaniline and *N*-(benzotriazol-2-ylmethyl)-*N*-methylaniline (molar ratio 84:16). To a solution of benzylmagnesium chloride prepared from benzyl chloride (2.30 ml, 20 mmol) and magnesium turnings (1.23 g, 30 mmol) in ether (30 ml) was added a solution of the isomeric mixture prepared above (2.38 g, 10 mmol) in THF (20 ml) in a rate to keep a gentle reflux. After being stirred at 25 °C for 24 h, the reaction mixture was poured into 10% ammonium chloride (100 ml), extracted with toluene (100 ml, 2 x 50 ml), washed with water (50 ml), 10% NaOH (50 ml), water (2 x 50 ml), and dried (Na_2CO_3).

Removal of the drying agent and solvent gave *N*-methyl-*N*-phenethylaniline (**2.10e**) as a yellow liquid, which was characterized by analysis and NMR (Tables 2.6-2.8).

Preparation of *N*-ethyl-*N*-phenethylaniline (**2.10f**). Compound **2.10f** was prepared similarly to compound **2.10e** and characterized by analysis and NMR (Tables 2.6-2.8).

Preparation of *N*-butyl-*N*-phenethylaniline (**2.10g**). To a stirred solution of benzotriazole (37.65 g, 316 mmol) and aniline (29.58 g, 316 mmol) in 95% ethanol (200 ml) was added butyraldehyde (27.61 g, 379 mmol). The mixture was stirred at 20 °C for 3 h, the precipitate formed was filtered off, washed with 1:1 ether/hexane (3 x 20 ml) and dried to give *N*-(1-benzotriazolylbutyl)aniline (**2.16**, 37.66 g, 45%). Compound **2.16** was dissolved in dry THF (150 ml) and refluxed with sodium borohydride (2.68 g, 70.7 mmol) for 27 h. The reaction mixture was washed with 10% NaOH (100 ml), extracted with chloroform (2 x 100 ml) and dried (Na_2CO_3). Removal of the drying agent and solvent afforded *N*-butylaniline (23.45 g) as a clear yellow liquid, which ^1H NMR spectrum was in agreement with the literature data [84T5185].

N-Butylaniline was converted to **2.8h** and subjected to a Grignard reaction with benzyl magnesium chloride, applying procedures similar to those for the preparation of **2.10e**, to give *N*-butyl-*N*-phenethylaniline (**2.10g**), which was characterized by analysis and NMR (Tables 2.6-2.8).

2.3 Preparation of Hindered Tertiary Aromatic Amines

2.3.1 Introduction

Preparation of tertiary aromatic amines with two secondary substituents at the nitrogen atom is generally difficult because of steric hindrance. A literature survey disclosed that almost all the published examples of such amines were the least

sterically hindered diisopropylamino derivatives. Reaction of sodium amide and bromobenzene with refluxing diisopropyl amine gave *N,N*-diisopropylaniline in 66% [69BSF1737] or 38% yield via a benzyne mechanism [72JOC137]. Catalytic reductive aminoalkylations of a mixture of primary aromatic amines with a ketone and its ketal under hydrogen pressures of 1000 psi at elevated temperatures were reported to give moderate to good yields of *N,N*-bis(*sec*-alkyl)amines [66USP3234281], e.g., *N,N*-diisopropylaniline in 56% yield. *N,N*-Bis(*sec*-butyl)aniline (**2.18**) was also claimed [66USP3234281] to be prepared but the yield was not given.

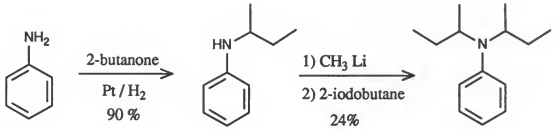
2.3.2 Results and Discussion

We attempted to prepare *N,N*-bis(*sec*-butyl)aniline (**2.18**) according to the literature procedure [66USP3234281] but failed. A mixture of 1 mole of aniline, 2 moles of 2,2-dimethoxybutane,* 2 moles of 2-butanone and 0.5 g of 1% platinum on alumina was stirred under a pressure of 1400 psi of hydrogen at 92-133 °C for 3 days to give a clean 86% yield of *N*-*sec*-butylaniline (**2.17**), but no *N,N*-bis(*sec*-butyl)aniline.

However, we were able to adapt a method described in 1960 for the preparation of *N,N*-diisopropyl-*o*-toluidine by alkylation of the lithium anion of *N*-isopropyl-*o*-toluidine with isopropyl iodide [60JA6163]. *N*-*sec*-Butylaniline (**2.17**) was conveniently prepared by reductive alkylation of aniline with butanone. Alkylation of the lithium salt of (**2.17**) with 2-iodobutane over 4 days in refluxing diethyl ether gave *N,N*-bis(*sec*-butyl)aniline (**2.18**) in 24% yield after conversion of the residual amine **2.17** to its benzamide (ca 70% recovery) and fractional distillation under reduced

* 2,2-dimethoxybutane was prepared by a modified procedure from Pfeiffer's method [31JA1043] because the literature method gave a mixture of the ketal and excess reagent trimethyl orthoformate which were difficult to separate due to their close boiling points. In our case, one equivalent trimethyl orthoformate was used to give 2,2-dimethoxybutane in 83% yield.

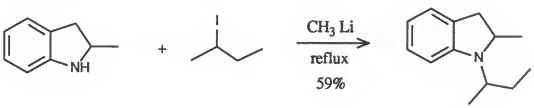
pressure (Scheme 2.5). The relatively low yield of the tertiary amine **2.18** reflects the higher steric hindrance of the *sec*-butyl groups compared with the diisopropyl groups of the literature compounds.



2.17 **2.18**

Scheme 2.5

Indoline **2.19** was similarly alkylated with 2-iodobutane to give 1-*sec*-butyl-2-methylindoline (**2.20**) in 59% yield. The only previous example of the *N*-alkylation of 2-methylindoline (**2.19**) was methylation to 2,3-dihydro-1,1,2-trimethylindolium iodide [58JCS2302].



2.19 **2.20**

Scheme 2.6

2.3.3 Experimental

Proton and carbon NMR spectra were obtained on a Varian VXR-300 instrument in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) as the internal standard. Coupling constants (J) were given in Hz. High resolution mass spectra were

recorded at 70 ev with an A.E.I. MS-30 mass spectrometer with a Kratos DS-55 data system. Diethyl ether was dried by refluxing with sodium and benzophenone and distilled immediately prior to use. Silica gel for column chromatography was 230-400 mesh. The model 4768 hydrogenation bomb was from the Parr Instrument Company, Illinois.

N-(1-Methylpropyl)aniline (**2.17**). Aniline (55.88 g, 0.60 mol), butanone (129.80 g, 1.80 mol) and 1% platinum on alumina (3.0 g) were placed in a hydrogenation bomb. The bomb was charged with hydrogen to a pressure of 1100 psi and the mixture was stirred at 100 °C for 2 days. The catalyst was filtered off, washed with 2-butanone and the excess ketone removed under reduced pressure at 80 °C to give *N*-(1-methylpropyl)aniline (**2.17**) (93.4 g, 90%) as an orange liquid (containing ca 2% of aniline).

N,N-Bis(1-methylpropyl)aniline (**2.18**). To a stirred solution of 1.4 M methyllithium in diethyl ether (433 ml, 0.606 mol) in dry diethyl ether (500 ml) under argon was added dropwise *N*-(*sec*-butyl)aniline (**2.17**) (83 g, 0.55 mol) over 5 h. The mixture was refluxed for 5 h., and 2-iodobutane (200 g, 1.09 mol) was added dropwise over 20 min.. After refluxing under argon for 4 days, the reaction was quenched with methanol (150 ml) and water (300 ml). The organic layer was separated and the aqueous layer was extracted with diethyl ether (400 ml). The combined organic layers were washed with water (500 ml) and dried (K_2CO_3). The solution was filtered and solvent removed under reduced pressure at 85 °C to yield an orange liquid (107.1 g). To a solution of the crude product in benzene (300 ml) was added anhydrous potassium carbonate (69 g, 0.5 mol) and benzoyl chloride (80 ml, 0.7 mol) and the obtained mixture was stirred under nitrogen for 20 h. Water (300 ml) was added and stirring continued for 1 h further. The product was washed with 20% sodium hydroxide (50 ml) followed by 10% sodium hydroxide (200 ml) and dried (Na_2CO_3). After removal of the

solvent the resulting deep brown liquid (163.4 g) was fractionally distilled to give i) 13.4 g, b.p. 40-80 °C/0.03 mm, shown by NMR to be *N,N*-bis(1-methylpropyl)aniline (**2.18**) 88% pure; ii) 16.6 g, b.p. 78-80 °C/0.03 mm, shown by NMR to be (**2.18**) 95% pure; iii) 15.6 g, shown by NMR to be *N-sec*-butyl-*N*-benzoylaniline more than 90% pure; and iv) 94.8 g, shown by NMR to be pure *N-sec*-butyl-*N*-benzoylaniline. Redistillation of fraction ii gave an analytical sample of the tertiary amine as a colorless liquid: b.p. 106-7 °C/1.7 mm. ^{1}H NMR (mixture of diastereomers): δ 7.15 (2 H, m), 6.83 (2 H, d, J = 8.8 Hz), 6.65-6.73 (1 H, m), 3.42 (2 H, m), 1.50-1.75 (4 H, m), 1.24 (6 H, d, J = 6.8 Hz), 0.91 (3 H, t, J = 7.4 Hz), 0.89 (3 H, t, J = 7.4 Hz). ^{13}C NMR (mixture of diastereomers): δ 11.97, 12.0, 18.5, 19.1, 28.6, 29.1, 54.5, 54.4, 116.8, 116.9, 117.4, 117.6, 128.4, 148.7, 148.8. HR MS calcd. for $C_{14}H_{23}N$: 205.1824. Found: 205.1830.

1-(1-Methylpropyl)-2-methylindoline (**2.20**). To a stirred solution of 1.4 M methyllithium in diethyl ether (180 ml, 252 mmol) diluted with diethyl ether (120 ml) under argon was added dropwise 2-methylindoline (**2.19**) (31.25 ml, 240 mmol). After reflux of the mixture for 3 h, 2-iodobutane (47.22 ml, 410 mmol) was added and the mixture was refluxed for 3 days further under argon. The excess methyllithium was destroyed by methanol (20 ml) and water (30 ml) and the organic layer was separated. The aqueous layer was extracted with ether (50 ml) and the combined organic layers were dried (K_2CO_3) and filtered. Acetic anhydride (40 ml) was added and the mixture was concentrated first on a water bath at 80-90 °C and then the excess acetic anhydride was removed under reduced pressure at 80-90 °C. The concentrate was dissolved in ether (100 ml) and washed with 20% potassium carbonate (4 x 20 ml) and 40% potassium carbonate (20 ml). After drying over anhydrous potassium carbonate and removal of the solvent at 70-90 °C a brownish yellow liquid (41.4 g) was obtained, which contained about 80% 1-(1-methylpropyl)-2-methylindoline (**2.20**). Fractional

distillation gave pure **2.20** (26.6 g, 59%) as a colorless liquid, b.p. 63-64 °C/0.03 mm. ^{1}H NMR (mixture of diastereomers): δ 6.95-7.20 (2 H, m, Ar), 6.51-6.59 (1 H, m, Ar), 6.38-6.46 (1 H, m, Ar), 3.70-3.90 (1 H, m, ring CH), 3.33 (0.5 H, sextet, J = 7.1 Hz, side chain CH), 3.15-3.25 (0.5 H, m, superimposed, side chain CH), 3.11-3.20 (1 H, m, ring CH_2), 2.50-2.60 (1 H, dd, ring CH_2), 1.70-1.85 (1 H, m, side chain CH_2), 1.48-1.62 (1 H, m, side chain CH_2), 1.25 (3 H, d, J = 6.1 Hz, 2-CH_3), 1.19 (3 H, t, J = 4.77 Hz, CH_3(CH), side chain), 0.95 {3 H, m, $CH_3(CH_2)$, side chain}. ^{13}C NMR (mixture of diastereomers): δ 11.88, 11.90, 16.4, 16.9, 22.0, 22.6, 27.5, 28.0, 37.5, 37.7, 53.5, 54.0, 56.3, 56.9, 106.9, 107.4, 116.0, 116.1, 124.1, 126.9, 127.1, 128.7, 128.9, 150.6, 151.1. HR MS calcd. for $C_{13}H_{19}N$: 189.15175. Found: 189.15175.

CHAPTER III
SYNTHETIC METHODS FOR ACYCLIC AND CYCLIC SULFONAMIDES

3.1 Foreword

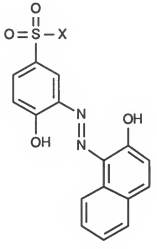
One important type of azo-dye precursors is 3-amino-4-hydroxybenzenesulfonamides. Thus, a new synthetic route to *N,N*-dialkylated sulfonamides of this type was developed. While 5- and 6-membered benzosultams can be prepared without difficulty, syntheses of benzosultams with larger rings are basically unknown (section 3.3.1). We now report a convenient synthetic method for 7- and 8-membered benzosultams.

3.2 Synthesis of Aminohydroxybenzenesulfonamides

3.2.1 Introduction

Acid Alizarin Violet N (**3.1a**) is a commonly used azo-dye with a number of applications (Scheme 3.1). A derivative of this dye, sulfonamide **3.1b** is used in the form of its chromium [79MI104025, 82MI112419, 85JAP6040157, 77JAP7763223] or cobalt [85MI124569, 76BEP841482, 84JAP59140264] complexes in dyeing leather, wool and synthetic polyamide fibers. Chromium and cobalt complexes of **3.1b** have been used recently in the production of electrostatographic toners [82JAP57167033, 84JAP5978361, 84JAP59188660, 84JAP5993457, 85EUP162632, 88JAP63216061]. The classical method for the preparation of 3-amino-4-hydroxybenzenesulfonamides is a multistep process involving chlorosulfonation of 2-chloronitrobenzene, amination of

the sulfonyl chloride obtained with ammonia, aromatic nucleophilic substitution of the chlorine atom with a hydroxy group and reduction of the nitro group [72HCA1509]. The application of **3.1b** as an azo-dye is limited by its relatively poor solubility in organic media. Azo-dyes of type **3.1c** and **3.1d** with two alkyl groups on the amido nitrogen are expected to have better solubities in organic solvents. We now report a new synthetic route to 3-amino-4-hydroxybenzenesulfonamides, which could be used for the preparation of azo-dyes with better solubilities (e.g., **3.1d**).



3.1a, $X = O^- Na^+$

3.1b, $X = NH_2$

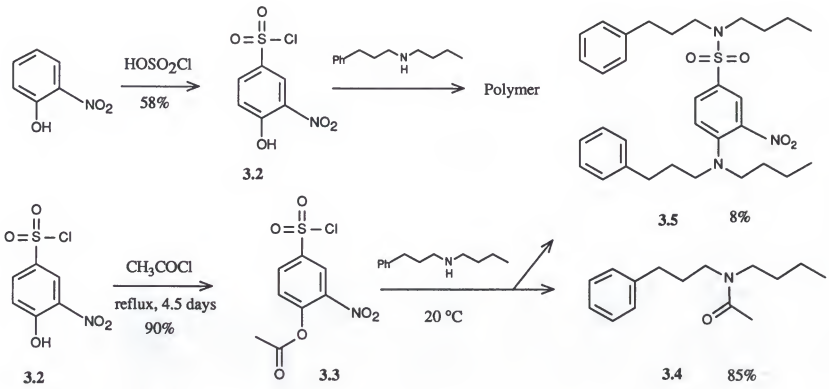
3.1c, $X = NBu_2$

3.1d, $X = N(Bu)CH_2CH_2CH_2Ph$

Scheme 3.1

3.2.2 Results and Discussion

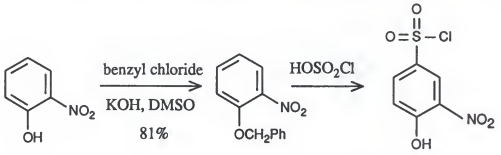
The *N,N*-dibutyl derivative **3.1c** was prepared from this laboratory, which included a Friedel-Crafts reaction of 2-nitrophenol with *N,N*-dibutylsulfamoyl chloride, reduction of the nitro group, and diazotization and coupling of the amine with 2-naphthol [UP]. Several attempts to extend this method to sulfonamide **3.1d** and other dyes of this type with aralkyl substituents on the sulfonamide nitrogen atom failed because of preferential intramolecular Friedel-Crafts reactions of the sulfamoyl chlorides to the corresponding sultams (see section 3.3).


HOSO2Cl
58%
Polymer
3.2
3.5
8%
CH3COCl
reflux, 4.5 days
90%
20 °C
3.2
3.3
3.4
85%

Scheme 3.2

An obvious preparation route would involve 4-hydroxy-3-nitro-benzenesulfonyl chloride (**3.2**), which was readily synthesized from 2-nitrophenol (Scheme 3.2). However, reaction of **3.2** with *N*-(3-phenylpropyl)-*N*-butylamine with or without the presence of a base under various conditions gave only polymeric materials. We concluded that the hydroxy group of **3.2** needed protection. Sulfonyl chloride **3.2** was therefore converted into the acetyl derivative **3.3** in high yield. Unfortunately, the *o*-nitro and *p*-chlorosulfonyl groups were so strongly electron-withdrawing that the most electrophilic site of **3.3** became the carbonyl carbon instead of the sulfur atom, and reaction of **3.3** with the amine at room temperature gave the acetamide **3.4** as the main product (85%). A small amount (8%) of a diaminated by-product (**3.5**) was also isolated, arising from substitution of the acetoxy group.

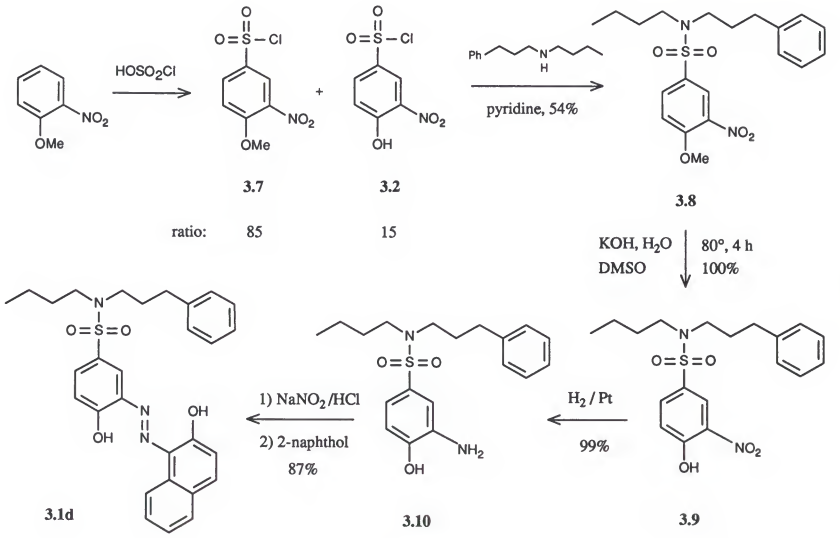
In another attempt, we benzylated the hydroxy group of 2-nitrophenol, obtaining compound **3.6** in 81% yield. However, when **3.6** was added very slowly to an excess of stirred chlorosulfonic acid cooled in an ice-salt bath and allowed to warm up, only **3.2** was obtained, evidently benzyl was too easily cleaved (Scheme 3.3).



3.6 **3.2**

Scheme 3.3

These experiments indicated that a methyl could be a suitable protecting group. Indeed, when 2-nitroanisole was treated with excess chlorosulfonic acid under mild


HOSO2Cl
NO2
OMe
O=S−Cl
O
NO2
OMe
3.7
+
O=S−Cl
O
NO2
OH
3.2
ratio: 85 15
Ph
N
H
pyridine, 54%
N
O=S=O
NO2
OMe
3.8
KOH, H2O
DMSO
80°, 4 h
100%
N
O=S=O
NO2
OH
3.9
H2 / Pt
99%
N
O=S=O
NH2
OH
3.10
1) NaNO2/HCl
2) 2-naphthol
87%
N
O=S=O
OH
N
N
OH
3.1d

Scheme 3.4

conditions, a mixture of 4-methoxy-3-nitrobenzenesulfonyl chloride (**3.7**) and its demethylated product (**3.2**) was obtained (Scheme 3.4). The most favorable ratio achieved of these two products was 85:15. The mixture was treated directly with *N*-(3-phenylpropyl)-*N*-butylamine in the presence of pyridine to give sulfonamide **3.8**. In this reaction, compound **3.2** formed a polymer, which was removed easily. Analytically pure **3.8** was obtained by column chromatography. Compound **3.8** was demethylated quantitatively by treatment with aqueous potassium hydroxide in dimethyl sulfoxide at 80 °C to give phenol **3.9**.

The nitro compound **3.9** was converted quantitatively to amine **3.10** by catalytic reduction with hydrogen under a pressure of 800 psi at room temperature. Amine **3.10** was diazotized and coupled with 2-naphthol under basic conditions to give directly the analytically pure azo compound, *N*-butyl-*N*-(3-phenylpropyl)-4-hydroxy-3-(2-hydroxy-1-naphthyl)azobenzenesulfonamide (**3.1d**), in high yield.

3.2.3 Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus or with a hot-stage microscope and were not corrected. Proton and carbon NMR spectra were obtained on a Varian VXR-300 instrument in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) as the internal standard. Coupling constants (J) were given in Hz. High resolution mass spectra were recorded at 70 ev with an A.E.I. MS-30 mass spectrometer with a Kratos DS-55 data system. Elemental analyses were performed under the supervision of Dr. David H. Powell. Silica gel for column chromatography was 230-400 mesh.

4-Hydroxy-3-nitrobenzenesulfonyl chloride (**3.2**). To stirred chlorosulfonic acid (6.0 ml, 90 mmol) cooled in an ice-water bath was added gradually 2-nitrophenol (4.17 g, 30 mmol) at a rate to keep the temperature below 10 °C. The mixture gradually

turned brown, a precipitate formed and bubbling occurred. After the bubbling stopped, the mixture was heated in an oil bath at 60 °C for 20 minutes. The black mixture was poured onto ice (50 g), extracted with chloroform (3 x 50 ml), washed with ice cold water (2 x 50 ml), dried over $MgSO_4$, filtered and the filtrate was concentrated under reduced pressure at 20 °C to afford pure **3.2** as a brown solid (4.12 g, 17.3 mmol, 58% yield), m.p. 48.5-50.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (1 H, d, J = 9.0 Hz), 8.22 (1 H, dd, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 8.83 (1 H, d, J = 2.4 Hz), 11.12 (1 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 122.2, 125.8, 132.8 (q), 134.7, 135.9 (q), 159.3 (q). HR MS calcd. for $C_6H_4ClNO_5S$ (M^+): 236.9499. Found: 236.9500.

Anal. Calcd. for $C_6H_4ClNO_5S$: C, 30.33; H, 1.70; N, 5.89. Found: C, 30.13; H, 1.60; N, 5.78.

4-Acetoxy-3-nitrobenzenesulfonyl chloride (**3.3**). A mixture of **3.2** (11.88 g, 50 mmol) and a large excess of acetyl chloride (20 ml) was refluxed in a round-bottom flask equipped with a Drierite drying tube. The reaction (monitored by NMR) took 4.5 days to complete. Excess acetyl chloride was removed by a rotary evaporator under reduced pressure and the residue was dried at 50 °C in a vacuum oven to afford **3.3** in a pure state as a dark brown solid (13.42 g, 45 mmol, 90% yield), m.p. 87.5-90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.44 (3 H, s), 7.56 (1 H, d, J = 8.7 Hz), 8.31 (1 H, dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz), 8.75 (1 H, d, J = 2.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8, 125.3, 127.3, 132.6, 141.9 (q), 148.9 (q), 167.5 (q).

Anal. Calcd. for $C_8H_6NClO_6S$: C, 34.36; H, 2.16; N, 5.01. Found: C, 34.22; H, 2.03; N, 4.91.

N-Butyl-*N*-(3-phenylpropyl)acetamide (**3.4**) and *N*-butyl-*N*-(3-phenylpropyl)-4-{*N*-butyl-*N*-(3-phenylpropyl)amino}-3-nitrobenzene-sulfonamide (**3.5**). To a stirred solution of 4-acetoxy-3-nitrobenzenesulfonyl chloride (**3.3**, 0.86 g, 3.08 mmol) in chloroform (5 ml) was added dropwise *N*-butyl-*N*-(3-phenylpropyl)amine (1.29 g,

6.77 mmol). The mixture became warm and a precipitate began to form. The mixture was stirred under nitrogen for 2 days and poured to water (50 ml), made basic (pH 9-10) with 40% K_2CO_3, and extracted with chloroform (2 x 40 ml). The organic solution was washed with water (3 x 10 ml), dried over anhydrous $MgSO_4$, filtered and concentrated to afford a yellow oil (1.22 g). The oil was separated by column chromatography (silica gel/chloroform) to afford **3.5** (0.14 g, 0.25 mmol, 8% yield) as a colorless oil, R_f 0.77 chloroform. ^1H NMR (300 MHz, $CDCl_3$): δ 0.85 (3 H, t, J = 7.9 Hz), 0.88 (3 H, t, J = 7.9 Hz), 1.17-1.35 (4 H, m), 1.43-1.58 (4 H, m), 1.83-1.96 (4 H, m), 2.57-2.64 (4 H, m), 3.09-3.24 (8 H, m), 7.00 (1 H, d, J = 9.0 Hz), 7.10-7.28 (10 H, m), 7.64 (1 H, dd, J_1 = 9.0 Hz, J_2 = 2.3 Hz), 8.11 (1 H, d, J = 2.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7 (2 C), 19.8, 19.9, 28.8, 29.4, 30.3, 30.8, 32.7, 32.9, 47.8, 48.2, 50.7, 51.9, 120.1, 126.0, 126.1, 126.4, 128.26 (2 C), 128.29 (2 C), 128.36, 128.42 (2), 128.44 (2 C), 130.9, 139.1, 140.9, 141.1, 147.1.

Anal. Calcd. for $C_{32}H_{43}N_3O_4S$: C, 67.93; H, 7.66; N, 7.43. Found: C, 68.10; H, 7.75; N, 7.30.

The second fraction afforded *N*-butyl-*N*-(3-phenylpropyl)acetamide (**3.4**, 0.61 g, 2.61 mmol, 85%) as a colorless liquid (a mixture of two conformers), R_f 0.02 chloroform. ^1H NMR (mixture of two conformers) (300 MHz, $CDCl_3$): δ 0.90 (3 H, t, J = 7.2 Hz), 0.93 (3 H, t, J = 7.2 Hz), 1.24-1.38 (4 H, m), 1.42-1.58 (4 H, m), 1.81-1.98 (4 H, m), 1.98 (3 H, s), 2.07 (3 H, s), 2.58-2.68 (4 H, m), 3.10-3.40 (8 H, m), 7.14-7.37 (10 H, m). ^{13}C NMR (mixture of two conformers) (75 MHz, $CDCl_3$): δ 13.7, 13.8, 20.0, 20.1, 21.4, 21.5, 29.2, 29.8, 30.2, 31.0, 32.9, 33.2, 45.4 (2 C), 48.0, 48.6, 125.8, 126.1, 128.1, 128.2, 128.3, 128.5, 140.7 (q), 141.7 (q), 170.0, 170.1. HR MS calcd. for $C_{15}H_{23}NO$ (M^+) 233.1780. Found: 233.1775.

2-Nitrophenyl benzyl ether [32JCS2876] (**3.6**). To a stirred mixture of 2-nitrophenol(13.91 g, 100 mmol) and DMSO (30 ml) was added KOH (6.17 g, 110

mmol), which dissolved quickly to give a hot red mixture. After cooling, benzyl chloride (11.51 ml, 100 mmol) was added and the mixture was stirred under nitrogen for 41 h. The product was dissolved in diethyl ether, washed thoroughly with water, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford **3.6** as a colorless liquid (18.68 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.18 (2 H,s), 6.99 (1 H, t, J = 8.4 Hz), 7.09 (1 H, d, J = 8.7 Hz), 7.30-7.50 (6 H, m), 7.80 (1 H, d, J = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 70.9, 115.0, 120.5, 125.5, 126.8 (2 C), 128.1, 128.6 (2 C), 134.0, 135.5, 140.1, 151.7. HR MS calcd. for $C_{13}H_{11}NO_3$ (M^++1, CI): 230.0817. Found: 230.0812.

N-Butyl-*N*-(3′-phenylpropyl)-4-methoxy-3-nitrobenzenesulfonamide (**3.8**). To stirred chlorosulfonic acid (5.32 ml, 80.0 mmol) cooled in an ice-water bath was added dropwise 2-nitroanisole (2.80 g, 18.3 mmol) at a rate to keep the temperature below 10 °C. After the addition, the ice bath was removed and the mixture was stirred at room temperature for 1 h. The dark red mixture was poured very slowly into stirred ice/water, extracted with diethyl ether, washed with water (3 x 20 ml), and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a mixture of 4-methoxy-3-nitrobenzenesulfonyl chloride (**3.7**) and 4-hydroxy-3-nitrobenzenesulfonyl chloride (**3.2**) (1.58 g, molar ratio 85:15) as a brown oil.

To a stirred mixture of the oil obtained above (1.51 g) and pyridine (5 ml) was added *N*-butyl-(3-phenylpropyl)amine (1.38 g, 7.20 mmol). The mixture was stirred for 30 h, poured into water and extracted with chloroform (100 ml). After washing with water (6 x 100 ml), drying over $MgSO_4$, and removal of the solvent, a red oil (1.95 g) was obtained. The oil was purified by column chromatography {silica gel/chloroform:hexane (1:1)} to give pure **3.8** (1.12 g, 2.76 mmol, 15% total yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (3 H, t, J = 7.3 Hz), 1.28 (2 H, sextet, J = 7.6 Hz), 1.48 (2 H, quintet, J = 7.6 Hz), 1.88 (2 H, quintet, J = 7.6 Hz), 2.62 (2 H, t, J = 7.6

Hz), 3.12 (2 H, t, J = 6.5 Hz), 3.15 (2 H, t, J = 6.5 Hz), 4.02 (3 H, s), 7.13-7.25 (4 H, m), 7.25-7.32 (2 H, m), 7.91 (1 H, dd, J_1 = 8.9 Hz, J_2 = 2.3 Hz), 8.22 (1 H, d, J = 2.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 19.8, 30.1, 30.6, 32.8, 47.6, 48.1, 57.0, 113.8, 124.8, 126.0, 128.2 (2 C), 128.4 (2 C), 132.2, 132.6, 139.1, 140.8, 155.3.

Anal. Calcd. for $C_{20}H_{26}N_2O_5S$: C, 59.10; H, 6.45; N, 6.89. Found: C, 59.16; H, 6.46; N, 6.85.

N-Butyl-*N*-(3′-phenylpropyl)-4-hydroxy-3-nitrobenzenesulfonamide (**3.9**). To a stirred solution of *N*-butyl-*N*-(3′-phenylpropyl)-4-methoxy-3-nitrobenzenesulfonamide (**3.8**, 0.73 g, 1.80 mmol) in DMSO (10 ml) was added 50% KOH (10 ml) and the mixture was stirred at 80 °C in an oil bath for 4 h. The mixture was poured into water, acidified to pH 4-5 with 20% HCl, and extracted with $CHCl_3$. The organic solution was washed with water, dried over $MgSO_4$, filtered, and concentrated to afford analytically pure **3.9** (0.71 g, 1.80 mmol, 100%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (3 H, t, J = 7.3 Hz), 1.12-1.35 (2 H, m), 1.43-1.54 (2 H, m), 1.81-1.95 (2 H, m), 2.61 (2 H, t, J = 7.6 Hz), 3.10-3.20 (4 H, m), 7.10-7.32 (6 H, m), 7.90 (1 H, dd, J_1 = 8.9 Hz, J_2 = 2.3 Hz), 8.53 (1 H, d, J = 2.3 Hz), 10.84 (1 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 19.8, 30.1, 30.6, 32.8, 47.5, 48.0, 121.1, 124.8, 126.1, 128.2 (2 C), 128.4 (2 C), 132.5, 132.8, 135.1, 140.8, 157.3.

Anal. Calcd. for $C_{19}H_{24}N_2O_5S$: C, 58.15; H, 6.16; N, 7.14. Found: C, 57.96; H, 6.23; N, 7.09.

N-Butyl-*N*-(3′-phenylpropyl)-3-amino-4-hydroxybenzenesulfonamide (**3.10**). A mixture of *N*-butyl-*N*-(3′-phenylpropyl)-4-hydroxy-3-nitrobenzenesulfonamide (**3.9**, 13.16 g, 33.53 mmol), 1% platinum on alumina (2 g), and ethanol (200 ml) was stirred at room temperature for 22 h in a bomb charged with 800 psi of hydrogen. The solution was filtered and concentrated to afford **3.10** as a colorless oil (12.02 g, 33.16 mmol, 99%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (3 H, t, J = 7.3 Hz), 1.25 (2 H, sextet, J = 7.5

Hz), 1.45 (2 H, quintet, J = 7.1 Hz), 1.84 (2 H, quintet, J = 7.3 Hz), 2.58 (2 H, t, J = 7.6 Hz), 3.10-3.14 (4 H, m), 4.2-5.4 (2 H, broad, NH_2), 6.76 (1 H, d, J = 8.1 Hz), 7.00 (1 H, dd, J_1 = 8.3 Hz, J_2 = 2.2 Hz), 7.06 (1 H, d, J = 2.2 Hz), 7.10-7.20 (4 H, m), 7.21-7.30 (2 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 19.8, 30.3, 30.8, 32.9, 47.9, 48.3, 114.1, 114.6, 118.7, 125.9, 128.28 (2 C), 128.35 (2 C), 130.5, 135.2, 141.2, 147.8. HR MS calcd. for $C_{19}H_{26}N_2O_3S$ (M^+): 362.1664. Found: 362.1664.

N-Butyl-*N*-(3-phenylpropyl)-4-hydroxy-3-(2-hydroxy-1-naphthyl)azobenzenesulfonamide (**3.1d**). To a stirred solution of *N*-butyl-*N*-(3′-phenylpropyl)-3-amino-4-hydroxybenzenesulfonamide (**3.10**, 7.41 g, 20.4 mmol) in ethanol (30 ml) cooled in an ice-salt-water bath were added 37% HCl (5.6 ml, 56 mmol) and ice (20 g). The mixture was diazotized by dropwise addition of a solution of sodium nitrite (1.54 g, 22.3 mmol) in water (10 ml) to give a yellow suspension.

To a solution of 2-naphthol (2.94 g, 20.4 mmol) in ethanol (40 ml) were added a solution of sodium hydroxide (1.48 g, 37 mmol) in water (15 ml) and a solution of sodium acetate (4.11 g, 50.0 mmol) in water (20 ml). The mixture was cooled in an ice-salt bath to 0 °C and the diazonium salt prepared above was added dropwise. The mixture immediately turned violet, and soon changed to violet-blue, and finally to red during the addition. The mixture was allowed to warm up and was stirred at room temperature for 19 h, diluted with water (200 ml) and stirred for 0.5 h. The red precipitate was collected, washed thoroughly with water, and dried in a vacuum oven at 70 °C for 12 h to give pure **3.1d** as a black powder (9.22 g, 17.8 mmol, 87% yield), m.p. 144-146 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (3 H, t, J = 7.3 Hz), 1.32 (2 H, sextet, J = 7.8 Hz), 1.49-1.55 (2 H, m), 1.65 (broad, 2 H), 1.89-1.94 (2 H, m), 2.64 (2 H, t, J = 7.6 Hz), 3.17 (2 H, t, J = 6.8 Hz), 3.19 (2 H, t, J = 6.8 Hz), &.14-7.22 (5 H, m), 7.24-7.34 (2 H, m), 7.50 (1 H, dt, J = 8.0, 1.0 Hz), 7.64-7.69 (2 H, m), 7.81 (1 H, d, J = 7.1 Hz), 7.90 (1 H, d, J = 9.0 Hz), 8.14 (1 H, d, J = 2.3 Hz), 8.18 (1 H, d, J = 8.1 Hz).

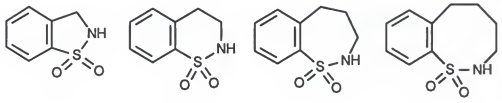
^{13}C NMR (75 MHz, acetone-d_6): δ 14.0, 20.4, 31.1, 31.4, 33.5, 48.5, 48.7, 116.3, 117.2, 122.2, 126.0, 126.5, 127.0, 127.1, 128.9, 129.0 (2 C), 129.2 (2 C), 129.7, 130.0, 131.3, 132.7, 133.0, 133.9, 141.6, 142.3, 152.6, 175.0.

Anal. Calcd. for $C_{29}H_{31}N_3O_4S$: C, 67.29; H, 6.04; N, 8.12. Found: C, 67.47; H, 6.09; N, 7.83.

3.3 Synthesis of Medium-sized Benzosultams

3.3.1 Introduction

The 5-membered benzosultams, especially 2,3-dihydro-1,2-benzisothiazole-1,1-dioxide (**3.11**) (Scheme 3.5) and its derivatives, are well known due to their relation to saccharin [77MI1363, 76MI1051, 78MI475, 86MI19]. Several *N*-substituted and 3-substituted derivatives [81USP4253865, 85EUP162494] or derivatives with substituents on the carbocyclic ring [89USP4842639, 87MI8707606] have been extensively studied as biologically active compounds. 2-alkyl-7-sulfonamido derivatives of (**3.11**) have been found to be effective herbicides [84EUP107979].



3.11 **3.12** **3.13** **3.14**

Scheme 3.5

Sultam **3.11** can be easily prepared by bromination of 2-methylbenzenesulfonyl chloride followed by treatment with ammonia [81USP4253865]. The simplest route to 3,4-dihydro-2*H*-benzothiazine-1,1-dioxide (**3.12**) involved hydrogenation of

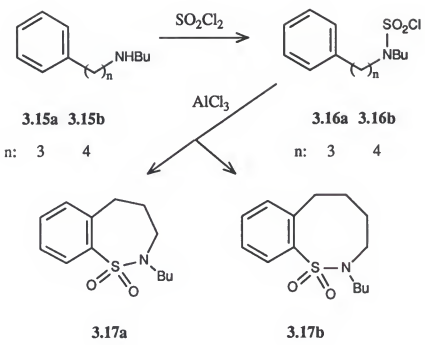
2-nitrobenzyl cyanide [50JA3047], diazotization of 2-aminobenzyl cyanide obtained and reaction with sulfur dioxide in the presence of copper (I) chloride, treatment of 2-cyanomethylbenzenesulfonyl chloride obtained with ammonia [70CB1991] and hydrogenation of the 2-cyanomethylbenzenesulfonamide intermediate [71CB1880].

Two alternative synthetic methods for **3.12** have also been reported [71CB1880]. Several derivatives of **3.12** are of interest for their anticonvulsant [73USP3770733], diuretic [63USP3113075] or sedative [71GEP2124953] activities. A 4-iodo derivative of 2,3,4,5-tetrahydrobenzo-1,2-thiazepine-1,2-dioxide (**3.13**) was obtained from iododediazonization of *o*-(*N*-2-propenylsulfamoyl)benzenediazonium tetrafluoroborate [87JOC1922].

3.3.2 Results and Discussion

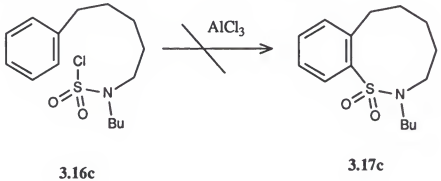
We now report a convenient synthetic method for *N*-alkyl derivatives of **3.13** and **3.14** by Friedel-Crafts cyclization of the corresponding ω-phenylalkanesulfamoyl chlorides. The related Friedel-Crafts cyclization of ω-phenylalkanesulfonyl chlorides [52JA974] gives cyclic sulfones in yields of 37, 76, 31 and 0% for 5-, 6-, 7- and 8-membered rings respectively.

N-Butyl-ω-phenylalkylamines **3.15** were prepared in almost quantitative yields by hydrogenation of a mixture of butylamine and hydrocinnamaldehyde, or a mixture of butyraldehyde and 4-phenylbutylamine with 1% platinum on alumina as the catalyst (Scheme 3.6). Upon treatment with sulfuryl chloride at 20 °C, amines **3.15** were converted to the corresponding sulfamoyl chlorides **3.16a** and **3.16b** in moderate separated yields. Friedel-Crafts intramolecular reactions of sulfamoyl chlorides **3.16** in nitrobenzene afforded sultams **3.17**. The analytically pure 7-membered ring sultam **3.17a** was obtained directly in 69% yield. Sultam **3.17b** (7% yield) was purified by column chromatography.



Scheme 3.6

Preliminary attempts to prepare the 9-membered ring sultam **3.17c** via **3.16c** under the same conditions were not successful (Scheme 3.7).



Scheme 3.7

3.3.3 Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus or with a hot-stage microscope and were not corrected. Proton and carbon NMR spectra were obtained on a Varian VXR-300 instrument in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) as the internal standard. Coupling constants (J) were given in Hz. High resolution mass spectra were recorded at 70 ev with an A.E.I. MS-30 mass spectrometer with a Kratos DS-55 data system. Microanalyses were performed by the Atlantic Microlab, Norcross, Georgia. Silica gel for column chromatography was 230-400 mesh.

N-Butyl-ω-phenylalkylamines **3.15. General procedure.** Butyraldehyde (8.8 ml, 100 mmol) was added portionwise to a solution of the appropriate amine (100 mmol) in methanol (150 ml) at 0 °C. The solution was placed in a Parr autoclave with the platinum catalyst (1% Pt on Al_2O_3, 0.5 g), the autoclave was charged with hydrogen to a pressure of 1250 psi, and the reduction was allowed to proceed overnight at 25 °C. The catalyst was filtered off and the solvent evaporated under reduced pressure to give pure amine **3.15b**. Amine **3.15a** was obtained in a similar manner from butylamine and 3-phenylpropanal.

N-Butyl-3-phenylpropylamine (**3.15a**). Oil, 91% yield. ^{1}H NMR: δ 7.24-7.30 (2 H, m), 7.15-7.20 (3 H, m), 2.55-2.68 (6 H, m), 1.81 (2 H, quintet, J = 7.8), 1.46 (2 H, quintet, J = 7.3), 1.34 (2 H, quintet, J = 7.4), 1.22 (1 H, S, NH), 0.91 (3 H, t, J = 7.3). ^{13}C NMR: δ 14.0, 20.5, 31.7, 32.3, 33.7, 49.6, 49.7, 125.7, 128.2 (2 C), 128.3 (2 C), 142.1. Hydrochloride, m.p. 218-19 °C (lit. m.p. 218-219 °C) [59JA3728].

N-Butyl-4-phenylbutylamine (**3.15b**). Oil, 93% yield. ^{1}H NMR: δ 7.24-7.32 (2 H, m), 7.15-7.20 (3 H, m), 2.54-2.72 (6 H, m), 1.25-1.70 (9 H, m), 0.91 (3 H, t, J = 7.3).

^{13}C NMR: δ 14.0, 20.5, 29.2, 29.8, 32.2, 35.8, 49.7, 49.9, 125.6, 128.2 (2 C), 128.3 (2 C), 142.4. Hydrochloride, m.p. 199-201 °C.

Anal. Calcd. for $C_{14}H_{24}NCl$: C, 69.54; H, 10.00; N, 5.79. Found: C, 69.68; H, 10.20; N, 5.74.

Sulfamoyl chloride **3.16**. General procedure. To a stirred solution of SO_2Cl_2 (16.2 ml, 200 mmol) in $CHCl_3$ (50 ml) cooled in an ice bath was added a mixture of triethylamine (13.9 ml, 100 mmol) and the appropriate amine **3.15** (100 mmol) at a rate to keep the temperature below 20 °C. After the addition was complete, the mixture was stirred at 25 °C for 2 h and then poured into 100 ml of ice-water. The organic phase was separated, washed with 10% HCl (50 ml) followed by ice-cold water (2 x 50 ml) and dried over anhydrous $CaCl_2$. After evaporation of the solvent, the residue was triturated with hexane, the hexane solution filtered and the solvent evaporated to give sulfamoyl chloride **3.16** of good purity, which was used directly in the next step. Sulfamoyl chlorides **3.16** were not stable enough to give CHN analyses, however, their HR MS were satisfactory.

N-Butyl-3-phenylpropanesulfamoyl chloride (**3.16a**). Oil, 42% yield. ^1H NMR: δ 7.29 (2 H, t, J = 7.6), 7.15-7.20 (3 H, m), 3.21-3.35 (4 H, m), 2.66 (2 H, t, J = 7.8), 2.02 (2 H, quintet, J = 7.5), 1.62 (2 H, quintet, J = 7.3), 1.33 (2 H, sextet, J = 7.8), 0.92 (3 H, t, J = 7.2). ^{13}C NMR: δ 13.5, 19.7, 28.9, 29.3, 32.7, 50.5, 50.9, 126.2, 128.2 (2 C), 128.5 (2 C), 140.4. HR MS Calcd. for $C_{13}H_{20}ClNO_2S$: 289.0903. Found: 289.0905

N-Butyl-4-phenylbutanesulfamoyl chloride (**3.16b**). Oil, 29% yield. ^1H NMR: δ 7.15-7.35 (5 H, m), 3.21-3.35 (6 H, m), 2.65 (2 H, t, J = 7.1), 1.58-1.80 (4 H, m), 1.33 (2 H, sextet, J = 7.6), 0.93 (3 H, t, J = 7.4). ^{13}C NMR: δ 13.5, 19.8, 26.8, 28.2, 29.3, 35.2, 50.8, 50.9, 125.9, 128.3 (2 C), 128.4 (2 C), 144.5. HR MS Calcd. for $C_{14}H_{22}NClOS$: 304.1138. Found: 304.1139.

Sultams **3.17**. General procedure. A solution of sulfamoyl chloride **3.16** (10 mmol) and anhydrous $AlCl_3$ (2.67 g, 20 mmol) in nitrobenzene (30 ml) was heated on an oil bath at 90 °C for 14 h. The reaction mixture was poured into ice-cold 10% HCl (50 ml) and extracted with ether (3 x 50 ml). The combined extracts were washed with water, 5% $NaHCO_3$, water again and dried ($MgSO_4$). The ether was evaporated and the nitrobenzene was distilled off under a pressure of 0.5 mm (from a water bath) to give sultam **3.17**. Compound **3.17a** was analytically pure, but **3.17b** required purification by column chromatography (silica gel, chloroform).

2-Butyl-1,2-benzothiazepine-1,1-dioxide (**3.17a**). Oil, 69% yield. ^{1}H NMR: δ 7.90 (1 H, d, J = 7.8), 7.41 (1 H, t, J = 7.4), 7.24-7.34 (2 H, m), 3.79 (2 H, s), 3.28 (2 H, s), 2.79 (2 H, s), 1.76 (2 H, quintet, J = 6.1), 1.52 (2 H, quintet, J = 8.4), 1.31 (2 H, sextet, J = 8.0), 0.89 (3 H, t, J = 7.3). ^{13}C NMR: δ 13.6, 19.6, 22.4, 30.6, 35.2, 45.8, 48.8, 126.2, 128.9, 131.3, 132.4, 139.4, 139.7.

Anal. Calcd. for $C_{13}H_{19}NO_2S$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.71; H, 7.57; N, 5.53.

3,4,5,6-Tetrahydro-2*H*-1,1-benzothiazocine-1,1-dioxide **3.17b**. Oil, 7% yield. ^{1}H NMR: δ 7.96 (1 H, dd, J = 8.4 and 1.7), 7.45 (1 H, dt, J = 7.4 and 1.7), 7.27-7.35 (2 H, m), 3.51-3.59 (2 H, m), 3.34 (2 H, t, J = 6.7), 2.87 (2 H, t, J = 7.3), 1.83 (2 H, quintet, J = 6.8), 1.56 (2 H, quintet, H, J = 7.8), 1.28-1.48 (4 H, m), 0.92 (3 H, t, J = 7.3). ^{13}C NMR: δ 13.7, 19.8, 21.9, 28.9, 30.3, 30.5, 43.9, 45.9, 125.9, 129.1, 132.0, 132.3, 139.6, 140.9.

Anal. Calcd. for $C_{14}H_{21}NO_2S$: C, 62.89; H, 7.92; N, 5.24. Found: C, 62.91; H, 7.91; N, 5.26.

CHAPTER IV
NOVEL CONVERSIONS OF BENZOTRIAZOL-1-YLMETHYL DERIVATIVES

4.1 Introduction

Formation of 1-hydroxymethylbenzotriazole (**4.1**) from the addition of benzotriazole to formaldehyde [34LA213] and its conversion by thionyl chloride to 1-chloromethylbenzotriazole (**4.2**) [52JA3868] are well known. Reaction of **4.2** with several classes of anions allowed the preparation of a variety of derivatives **4.3,** where X is a group linked by an oxygen, sulfur or nitrogen atom [87JCS(P1)781]. We now report the synthesis of further novel compounds of type **4.3.**

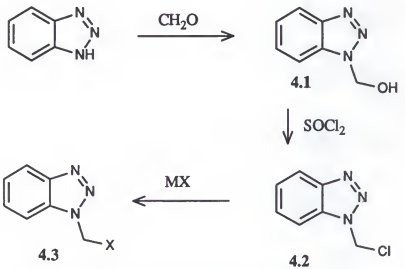
Benzotriazole derivatives of the type $BtCH_2COR$ prepared from benzotriazole and the appropriate bromo or chloro compounds have been known since 1935 [35LA113], but none of their reactions have been reported. We studied two such compounds: derivatives of ethyl acetate **4.4** [70T497] and acetophenone **4.13** [90AJC133].

4.2 Result and Discussion

4.2.1 Compounds of Type $BtCH_2X$

It was found that the chlorine atom of 1-chloromethylbenzotriazole (**4.2**) was readily substituted with bromine (**4.3a**) or iodine (**4.3b**) by treatment of **4.2** in acetone with sodium bromide or iodide respectively (Scheme 4.1). The bromo derivative **4.3a**

was relatively stable but the iodo derivative **4.3b** was sensitive to moisture or light. The reactivity of **4.2** towards nucleophiles was enhanced by using silver instead of sodium salts: thus, treatment with silver nitrate produced (benzotriazol-1-yl)methyl nitrate (**4.3c**) in 72% yield.

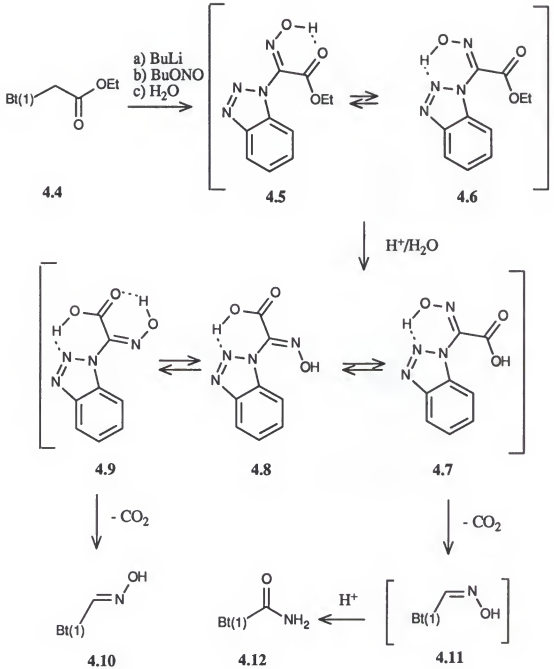


4.3a, MX = NaBr; **4.3b**, MX = NaI; **4.3c**, MX = $AgONO_2$

Scheme 4.1

4.2.2 Reaction of $BtCH_2COOEt$ with Butyl Nitrite

Treatment of lithiated ethyl (benzotriazol-1-yl)acetate **4.4** with butyl nitrite produced oxime **4.10**, or amide **4.12**, in moderate yields (Scheme 4.2). NMR spectra of the crude reaction mixtures revealed the presence of both compounds in ratios dependent on work-up conditions. When the reaction mixture was treated with water followed by acidification with dilute sulfuric acid, oxime **4.10** was formed as the main product. The use of diethyl ether for extraction enabled us to separate **4.10** in a relatively pure state since amide **4.12** is insoluble in ether. However, when the reaction mixture was gently treated with acetic acid, amide **4.12** was isolated as the main product.



4.4 **4.5** **4.6** **4.9** **4.8** **4.7** **4.10** **4.12** **4.11**

Bt(1) = benzotriazol-1-yl

Scheme 4.2

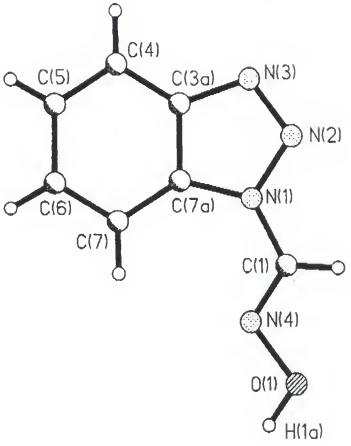


Figure 4.1 X-Ray Structure and Labelling of Oxime **4.10**.

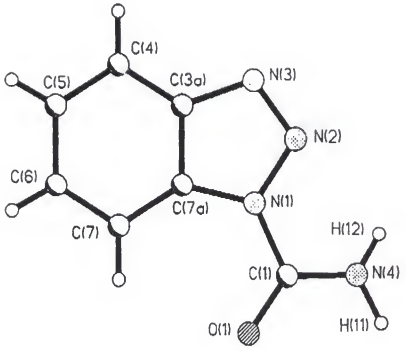


Figure 4.2 X-Ray Structure and Labelling of Amide **4.12**.

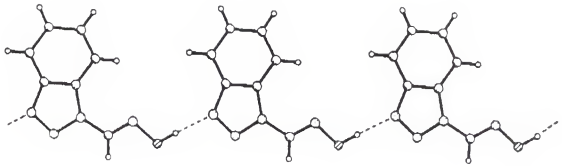


Figure 4.3 Intermolecular Hydrogen Bonding in Oxime **4.10**.

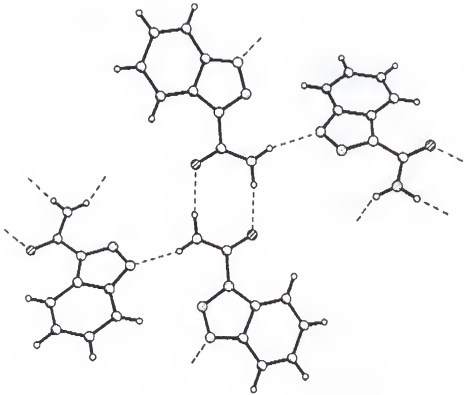


Figure 4.4 Intermolecular Hydrogen Bonding in Amide **4.12**.

We rationalize this phenomenon as follows. In the first step, a mixture of the *E* (**4.5**) and *Z* (**4.6**) esters is formed. Both forms are stabilized by intramolecular hydrogen bonds, however, the hydrogen bonding of **4.6** (OH---N) should be stronger than that of **4.5** (OH---O) due to the stronger basicity of the nitrogen atom. When isomer **4.6** is predominant, hydrolysis of the ester formed under mild conditions should lead to acid **4.7** (or **4.8**), which spontaneously undergoes decarboxylation to the *Z* oxime **4.11**. Beckmann rearrangement of **4.11** (the benzotriazolyl group seems to facilitate such reaction) leads to amide **4.12** as the main product.

Hydrolysis of the isomeric ester **4.5** gives acid **4.9**. Two strong intramolecular hydrogen bonds of **4.9** stabilize it more than **4.7** and **4.8**. Under strongly acidic conditions forms **4.7** and **4.8** isomerize to **4.9** making it predominant in the mixture. Decarboxylation of the *E* acid (**4.9**) produces the *E* oxime (**4.10**). *Cis*-Orientation of the proton and the hydroxy group in **4.10** prevents its Beckmann rearrangement [60OR(11)1] and oxime **4.10** is isolated as the main product. *X*-Ray crystallographic data proved the *E* configuration of **4.10** and the molecular structure of amide **4.12**.

Figures 4.1 and 4.2 show perspective views and atom labelling of the structures of oxime **4.10** and amide **4.12** respectively. Tables 4.1, 4.2 and 4.3 list atom coordinates and bonding geometries. The structure of **4.10** is confirmed as the trans isomer, which exists in the solid state in an anti conformation about the N1-C1 bond. The benzotriazole ring system is planar to within 0.016 Å and is approximately coplanar with the oxime moiety (angle between mean planes = 12.9(5)°). As shown in Figure 4.3 the molecules pack in chains with the OH group hydrogen bonded to N3 of an adjacent molecule related by a *C*-centering (O1---N3' = 2.790(7) Å, H1A--- N3' = 1.85(6) Å, O1-H1A---N3' = 176(5)°).

Amide **4.12** exists in the solid state in a conformation with the amide group nearly coplanar with the benzotriazole system (angle between meanplanes = 10.6(2)°)

Table 4.1 Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Coefficients ($Å^2$ x 10^3) for Oxime **4.10**.

atom	x	y	z	U_{eq}[a]
N(1)	4623[b]	-783(5)	2856[b]	21(3)
N(2)	4297(8)	-2046(5)	2082(10)	25(3)
N(3)	3056(7)	-2023(4)	6(10)	26(3)
C(3A)	2534(7)	-737(6)	-608(11)	24(4)
C(4)	1286(10)	-232(6)	-2637(13)	29(4)
C(5)	1091(9)	1100(6)	-2761(12)	33(4)
C(6)	2128(9)	1933(5)	-923(12)	28(4)
C(7)	3364(8)	1436(5)	1094(12)	23(4)
C(7A)	3548(10)	80(4)	1194(13)	19(3)
C(1)	5950(8)	-556(7)	5034(12)	24(4)
N(4)	6160(7)	560(5)	5862(10)	24(3)
O(1)	7574(7)	563(4)	8032(9)	31(2)

a) Equivalent isotropic U defined as one third of the trace of the orthoganalized U_{ij} tensor.

b) Origin definding parameter.

Table 4.2 Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Coefficients ($Å^2$ x 10^3) for Amide **4.12**.

atom	x	y	z	U_{eq} [a]
N(1)	1753(2)	6377(2)	4306(1)	24(1)
N(2)	1829(2)	6096(2)	3206(1)	29(1)
N(3)	2510(2)	4658(2)	3164(1)	30(1)
C(3A)	2901(3)	3955(3)	4248(2)	26(1)
C(4)	3668(3)	2440(3)	4625(2)	32(1)
C(5)	3916(3)	2081(3)	5762(2)	36(1)
C(6)	3420(3)	3193(3)	6507(2)	35(1)
C(7)	2655(3)	4690(3)	6144(2)	29(1)
C(7A)	2408(2)	5048(2)	4990(2)	23(1)
C(1)	1117(3)	7903(2)	4624(2)	26(1)
N(4)	866(2)	9056(2)	3832(1)	32(1)
O(1)	867(2)	8008(2)	5573(1)	33(1)

a Equivalent isotropic U defined as one third of the trace of the orthoganalized U_{ij} tensor.

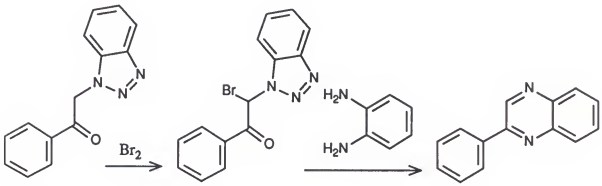
Table 4.3 Bond Lengths (Å) and Angles (°).

atoms	oxime **4.10**	amide **4.12**	atoms	oxime **4.10**	amide **4.12**
N(1)-N(2)	1.375(7)	1.374(2)	N(1)-N(7A)	1.393(6)	1.380(2)
N(1)-C(1)	1.404(6)	1.435(3)	N(2)-N(3)	1.312(7)	1.298(2)
N(3)-C(3A)	1.395(8)	1.394(3)	C(3A)-C(4)	1.393(8)	1.398(3)
C(3A)-C(7A)	1.398(8)	1.396(3)	C(4)-C(5)	1.371(9)	1.375(3)
C(5)-C(6)	1.427(9)	1.411(3)	C(6)-C(7)	1.381(8)	1.380(3)
C(7)-C(7A)	1.396(7)	1.396(3)	C(1)-N(4)	1.263(9)	1.327(3)
N(4)-O(1)	1.413(7)		C(1)-O(1)		1.223(3)
N(2)-N(1)-C(7A)	110.5(3)	110.4(2)	N(2)-N(1)-C(1)	118.3(4)	121.1(2)
C(7A)-N(1)-C(1)	131.1(5)	128.5(2)	N(1)-N(2)-N(3)	108.0(4)	108.4(2)
N(2)-N(3)-C(3A)	109.2(5)	108.9(2)	N(3)-C(3A)-C(4)	129.9(6)	129.8(2)
N(3)-C(3A)-C(7A)	108.6(5)	108.6(2)	C(4)-C(3A)-C(7A)	121.4(6)	121.6(2)
C(3A)-C(4)-C(5)	116.6(6)	116.8(2)	C(4)-C(5)-C(6)	121.9(6)	121.3(2)
C(5)-C(6)-C(7)	121.6(5)	122.4(2)	C(6)-C(7)-C(7A)	115.7(5)	116.0(2)
N(1)-C(7A)-C(3A)	103.7(4)	103.7(2)	N(1)-C(7A)-C(7)	133.6(6)	134.4(2)
C(3A)-C(7A)-C(7)	122.7(5)	121.9(2)	N(1)-C(1)-N(4)	119.0(6)	114.9(2)
C(1)-N(4)-O(1)	108.8(5)		N(1)-C(1)-O(1)		117.8(2)
N(4)-C(1)-O(1)		127.2(2)			

and with the NH_2 group syn to N_2 of the benzotriazole. The benzotriazole system is planar to within 0.011 Å and has similar bonding geometry to that in the oxime. As shown in Figure 4.4, there is a system of intermolecular hydrogen bonding that interconnects the molecules in a three-dimensional network. In particular the molecules are connected about a center of inversion by a dimeric NH---O hydrogen bond (N4---O1' = 2.935(3) Å, H11---O1' = 1.99(3) , N4-H11---O1' = 171(2)°). In addition, the remaining NH_2 hydrogen is weakly bonded to N3 of an adjacent molecule related by a 2-fold screw axis (N4---N3" = 3.052(3) Å, H12---N3" = 2.20(3) Å, N4-H12---N3" = 158(2)°).

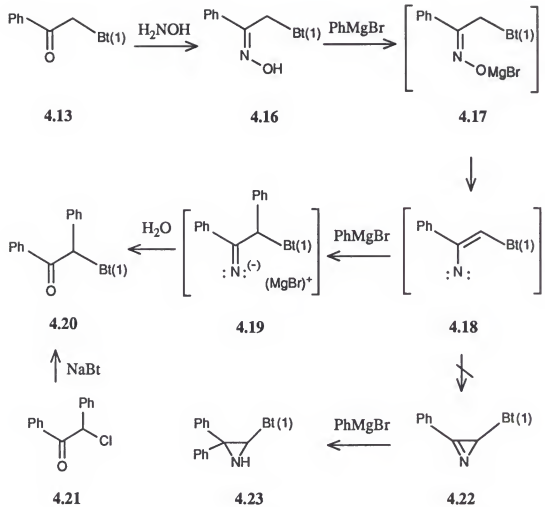
4.2.3 Conversions of $BtCH_2COPh$

The α,α-disubstituted ketone **4.14** [92ACS] derived from α-(benzotriazol-1-yl)-acetophenone (**4.13**) was demonstrated to be a protected form of phenylglyoxal, which with *o*-phenylenediamine formed 2-phenylquinoxaline (**4.15**) [80JHC1559] (Scheme 4.3).



4.13 **4.14** **4.15**

Scheme 4.3



Bt(1) = benzotriazol-1-yl

Scheme 4.4

Oxime **4.16** reacted with phenylmagnesium bromide to give a complex mixture from which compound **4.20** was isolated in 8% yield (Scheme 4.4). To prove the structure of **4.20**, it was prepared directly by the reaction of desyl chloride (**4.21**) with sodium benzotriazolide. Upon treatment with an excess of the Grignard reagent (reacting as a strong base), salt **4.17** evidently decomposed to nitrene **4.18** in analogy to the mechanism proposed for the Hoch-Campbell reaction [B-84MI(7)85]. However, nitrene **4.18** was stabilized by benzotriazol-1-yl group through resonance and did not undergo spontaneous cyclization to azirine **4.22**, which might have reacted further with PhMgBr to give aziridine **4.23**, but reacted further with the Grignard reagent to give iminium salt **4.19**, which hydrolyzed during the work-up to **4.20**.

4.3 Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus or with a hot-stage microscope and were not corrected. Proton and carbon NMR spectra were obtained on a Varian VXR-300 instrument in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) as the internal standard. Coupling constants (J) were given in Hz. Assignments of the ^{13}C NMR spectra (*C*-4, *C*-5, etc.) refer to the benzotriazolyl carbon atoms. High resolution mass spectra were recorded at 70 ev with an A.E.I. MS-30 mass spectrometer with a Kratos DS-55 data system. Elemental analyses were performed under the supervision of Dr. David H. Powell. Silica gel for column chromatography was 230-400 mesh. Compounds **4.4** [70T497], **4.13** [90AJC133] and **4.14** [92ACS] were obtained according to the literature procedures cited.

X-Ray crystallography. Intensity data were collected at -80 °C with a Nicolet R3m four-circle diffractometer by using monochromatized Mo Kα (λ = 0.71073 Å) radiation. The crystals used were a colorless needle of dimensions 0.60 x 0.06 x 0.05

mm of oxime **4.10** and a fawn plate of dimensions 0.58 x 0.32 x 0.08 of amide **4.12**. Cell parameters were determined by least squares refinement, the setting angles of 25 accurately centered reflections ($2\Theta > 15°$) being used. Throughout data collections the intensities of three standard reflections were monitored at regular intervals and this indicated no significant crystal decomposition. The space groups followed from systematic absences and data statistics. The intensities were corrected for Lorentz and polarization effects but not for absorption. Reflections with $I > 2.5\sigma(I)$ and $I > 3\sigma(I)$, for oxime 11 and amide 13 respectively, were used for structure solution and refinement.

The structures were solved by direct methods, and refined by full-matrix least-squares procedures. All non-hydrogen atoms were refined with anisotropic displacement coefficients. The N-H and O-H hydrogens were located from difference Fourier syntheses, whereas the C-H hydrogen atoms were included in calculated positions. All hydrogens were assigned isotropic displacement coefficients. The functions minimized were $\Sigma w(|F_o| - |F_c|)^2$, with $w = [\sigma^2(F_o) + 0.0005F_o^2]^{-1}$. The absolute configuration of oxime **4.10** was not determined. Final difference maps showed no features greater or less than $0.35e^-/Å^3$. Final non-hydrogen atom coordinates, bond lengths and bond angles are listed in Tables 1 and 2. Tabulations of hydrogen atom coordinates, anisotropic thermal parameters, structure factors and equations of meanplanes are available as supplementary material [92ACS].

Crystal data for oxime **4.10** at -80 °C: $C_7H_6N_4O$, Mr = 162.2, monoclinic, space group Cc, a = 11.835(7), b = 10.210(4), c = 8.198(4) Å, b = 131.80(3)°, U = 738.5(6) $Å^3$, F(000) = 336, Z = 4, D_c = 1.46 g cm^{-3}, μ(Mo-Kα) = 1.0 cm^{-1}, ω scans, $2\Theta_{max} = 60°$, N = 1134, N_o = 569, 107 parameters, S = 1.11, R = 0.047, R_w = 0.047.

Crystal data for amide **4.12** at -80 °C: $C_7H_6N_4O$, Mr = 162.2, monoclinic, space group $P2_1/n$, a = 7.607(2), b = 8.222(2), c = 12.160(3) Å, β = 105.98(2)°, U = 731.2(4)

$Å^3$, F(000) = 336, Z = 4, D_c = 1.47 g cm^{-3}, μ(Mo-Kα) = 1.0 cm^{-1}, ω scans, $2\Theta_{max}$ = 60°, N = 2131, N_o = 1258, 109 parameters, S = 1.41, R = 0.045, R_w = 0.053.

1-Bromomethylbenzotriazole (**4.3a**). A mixture of 1-chloromethylbenzotriazole (**4.2**) (10.00 g, 60.0 mmol) and sodium bromide (961.4 g, 60.0 mmol) in acetone (120 ml) was stirred at room temperature for 21 h. The solution was filtered and stirred with additional sodium bromide (20.0 g, 12.0 mmol) for 3 days. The solution was filtered and stirred again with sodium bromide (70.0 g, 68.0 mmol) for 4 more days to convert 2 to pure **4.3a** as a white solid (9.66 g, 45.6 mmol, 76%), m.p. 113-115.5 °C. ^{1}H NMR: δ 6.42 (2 H, s), 7.46 (1 H, t, J = 8.2 Hz), 7.62 (1 H, t, J = 8.3 Hz), 7.68 (1 H, d, J = 8.3 Hz), 8.11 (1 H, d, J = 8.4 Hz). ^{13}C NMR: δ 39.2 (CH_2), 109.8 (C-7), 120.5 (C-4), 125.0 (C-5), 128.5 (C-6), 131.9 (C-7a), 146.5 (C-3a).

Anal. Calcd. for $C_7H_6BrN_3$: C, 39.65; H, 2.85; N, 19.82. Found: C, 39.70; H, 2.75; N, 20.15.

1-Iodomethylbenzotriazole (**4.3b**). A mixture of (**4.2**) (10.00 g, 60.0 mmol) and sodium iodide (35.8 g, 239 mmol) in acetone (120 ml) was stirred for 15 min. The solution was filtered, the solvent evaporated at room temperature, and the residue extracted with chloroform (200 ml) followed by evaporation of the solvent to give pure 1-iodomethylbenzotriazole (**4.3b**) as a yellow solid (13.51 g, 52.2 mmol, 87%), m.p. 101-103 °C. ^{1}H NMR: δ 6.46 (2 H, s), 7.43-7.50 (1 H, m), 7.60-7.68 (2 H, m), 8.10 (1 H, d, J = 8.4 Hz). ^{13}C NMR: δ 9.5 (CH_2), 110.2 (C-7), 120.5 (C-4), 124.9 (C-5), 128.2 (C-6), 131.7 (C-7a), 146.6 (C-3a).

Anal. Calcd. for $C_7H_6IN_3$: C, 32.46; H, 2.33; N, 16.22. Found: C, 32.07; H, 2.19; N, 16.23.

(Benzotriazol-1-yl)methyl nitrate (**4.3c**). To a stirred solution of 1-chloromethylbenzotriazole (**4.2**) (1.00 g, 6.51 mmol) in acetone (10 ml, distilled from phosphorous pentoxide) was added silver nitrate powder (1.11 g, 6.51 mmol) and the

mixture was stirred for 11 h. The mixture was filtered and the solvent evaporated under reduced pressure at 33 °C to give the crude product (**4.3c**) (0.91 g, 72% yield) as a pale yellow oil. A portion of the crude product was subjected to column chromatography ($CHCl_3$-toluene 1:2) to afford analytically pure **4.3c** as a colorless oil. ^{1}H NMR: δ 6.90 (2 H, s), 7.44 (1 H, t, J = 8.2 Hz), 7.60 (1 H, t, J = 8.1 Hz), 7.72 (1 H, d, J = 8.3 Hz), 8.08 (1 H, d, J = 8.4 Hz). ^{13}C NMR: δ 74.0 (CH_2), 109.3 (C-7), 120.2 (C-4), 124.0 (C-5), 128.9 (C-6), 132.5 (C-7a), 145.9 (C-3a). IR (film): 3037, 2970, 1664, 1615, 1495, 1455, 1290, 1161, 1003, 949, 833, 789, 748 cm^{-1}. HR MS: Calcd. $C_7H_6N_4O_3$: 194.0440. Found: 194.0434.

(*E*)-(Benzotriazol-1-yl)formaldoxime (**4.10**). To a solution of **4.4** (2.05 g, 10.0 mmol) in THF (30 ml) was added 2.5 M butyllithium in hexane (4.40 ml, 11.0 mmol) dropwise with stirring and external cooling with dry ice-acetone. Butyl nitrite (1.2 g, 12 mmol) was introduced slowly while maintaining the reaction temperature at -78 °C. The mixture was stirred for 1 h and allowed to warm to room temperature. After stirring for additional 5 h, the solvent was evaporated under reduced pressure at 30-35 °C and the residue triturated with water (30 ml). The aqueous solution was acidified with 1 N sulfuric acid and extracted twice with diethyl ether. The solvent was evaporated and the residue triturated with ethyl acetate (5 ml). The crude product was collected and recrystallized from ethanol to give **4.10** as needles (0.6 g, 3.7 mmol, 37%), m.p. 160-161 °C. ^{1}H NMR (DMSO-d_6): δ 7.57 (1 H, dd, J = 7.0, 8.3 Hz), 7.74 (1 H, dd, J = 7.0, 8.3 Hz), 8.13 (1 H, d, J = 8.3 Hz), 8.19 (1 H, d, J = 8.4 Hz), 9.52 (1 H, s, N:CH), 11.57 (1 H, s, OH). ^{13}C NMR (DMSO-d_6): δ 113.1 (C-7), 119.6 (C-4), 125.6 (C-5), 129.3 (C-6), 129.9 (C-7a), 142.4 (N:CH), 145.5 (C-3a).

Anal. Calcd. for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.55. Found: C, 51.57; H, 3.58; N, 34.50.

(Benzotriazol-1-yl)formamide (**4.12**). To a stirred solution of **4.4** (10.26 g, 50.0 mmol) in THF (150 ml) at -78 °C under argon was added dropwise 2.5 M butyllithium in hexane (22.0 ml, 55.0 mmol) and the mixture was stirred for 1 h. Butyl nitrite (6.43 ml, 55.0 mmol) was added dropwise and the mixture was allowed to warm to room temperature overnight. The solvents were removed at 35 °C under reduced pressure and water (20 ml) was added. The mixture became hot and the solid dissolved completely. The solution was acidified to pH 4-5 with acetic acid, extracted with ethyl acetate (2 x 30 ml), dried (Na_2SO_4) and the solvent evaporated to give a yellowish brown mixture of a liquid and a solid. The solid was filtered off, washed with diethyl ether, and triturated with hot ethanol to give **4.12** as brown needles (0.44 g, 14.0 mmol, 28%), m.p. 160-2 °C (decomp.). ^{1}H NMR (DMSO-d_6): δ 7.54 (1 H, t, J = 7.7 Hz), 7.71 (1 H, t, J = 7.7 Hz), 8.19 (1 H, d, J = 8.3 Hz), 8.25 (1 H, d, J = 8.3 Hz), 8.31 (1 H, bs, NH), 8.60 (1 H, bs, NH). ^{13}C NMR (DMSO-d_6): δ 113.7 (C-7), 119.5 (C-4), 125.2 (C-5), 129.5 (C-6), 131.3 (C-7a), 145.6 (C-3a), 149.9 (C:O).

Anal. Calcd. for $C_7H_6N_4O$: C, 51.85; H, 3.73; N, 34.55. Found: C, 51.69; H, 3.63; N, 34.95.

2-Phenylquinoxaline (**4.15**). A mixture of **4.14** (0.32 g, 1.00 mmol) and *o*-phenylenediamine (0.11 g, 1.00 mmol) in a test tube was immersed in an oil bath at 150 °C, heated to 192 °C over 80 min. (until the mixture melted) and kept at 192-5 °C for 30 min. The mixture was allowed to cool, dissolved in chloroform, washed with 20% NaOH (2 x), water (3 x) and dried (Na_2CO_3). The red glassy residue (0.18) was subjected to column chromatography (toluene) to give **4.15** as brown needles (0.03 g, 0.15 mmol, 15%), m.p. 68-74 °C, lit. 75 °C [80JHC1559]. ^{1}H NMR: δ 7.50-7.60 (3 H, m), 7.72-7.82 (2 H, m), 8.10-8.25 (4 H, m), 9.32 (1 H, s). ^{13}C NMR: δ 127.5 (2 C), 129.09 (2 C), 129.07, 129.5, 129.6, 130.1, 130.2, 136.7, 141.5, 142.2, 143.3, 151.8. HR MS: Calcd. $C_{14}H_{10}N_2$: 206.0844. Found: 206.0839.

α-(Benzotriazol-1-yl)acetophenone oxime (**4.16**). To a solution of hydroxylamine hydrochloride (4.86 g, 70.0 mmol) in water (20 ml) was added 10% NaOH (20 ml) and **4.13** (1.75 g, 7.37 mmol) in ethanol (60 ml). The mixture was stirred under reflux for 1 h and at 25 °C overnight. The crystals formed were filtered off, washed thoroughly with water, and dried to give pure α-(benzotriazol-1-yl)acetophenone oxime (**4.16**) as microcrystalls (1.42 g, 5.63 mmol, 76%), m.p. 223-225 °C. ^{1}H NMR (DMSO-d_6): δ 6.09 (CH_2, 2 H, s), 7.30-7.40 (4 H, m), 7.56 (1 H, t, J = 7.6 Hz), 7.71-7.73 (2 H, m), 7.84 (H-7, 1 H, d, J = 8.3 Hz), 8.00 (H-4, 1 H, d, J = 8.1 Hz), 12.20 (OH, 1 H, s). ^{13}C NMR (DMSO-d_6): δ 41.0 (CH_2), 110.4 (C-7), 119.1 (C-4), 124.0 (C-5), 126.2 (2 C, ortho), 127.4, 128.3 (2 C, meta), 129.1, 132.8, 133.9, 144.8 (C-3a), 150.7 (C:N).

Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.66; H, 4.79; N, 22.21. Found: C, 66.27; H, 4.71; N, 22.32.

α-(Benzotriazol-1-yl)-α-phenylacetophenone (**4.20**). Method A. To a solution of phenyl magnesium bromide (from bromobenzene, 4.32 ml, 41.0 mmol) in diethyl ether (20 ml) under argon was added **4.16** (1.55 g, 6.15 mmol). After addition of toluene (40 ml), diethyl ether was distilled off and the mixture refluxed for 2 h. The product was poured to a mixture of ice and water (100 ml), acidified (pH 5) with acetic acid, extracted with chloroform (2 x 70 ml), and the organic phase washed with water (2 x 100 ml) and dried ($MgSO_4$). After removal of the solvent a dark brown viscous oil (2.10 g) was obtained, which was subjected to column chromatography (chloroform) to give **4.20** (R_f 0.43) as needles (0.15 g, 0.48 mmol, 8%), m.p. 161-163 °C. ^{1}H NMR: δ 7.21-7.46 (10 H, m), 7.57 (1 H, t, J = 7.3 Hz), 7.88 (s, 1 H), 7.99-8.05 (3 H, m). ^{13}C NMR: δ 68.1 (PhCHBt), 111.4 (C-7), 119.9 (C-4), 123.8 (C-5), 127.5 (C-6), 128.9, 129.0, 129.1, 129.3, 129.4, 132.9, 133.1, 134.2, 134.4, 146.6 (C-3a), 192.6 (C:O).

Anal. Calcd. for $C_{20}H_{15}N_3O$: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.56; H, 4.81; N, 13.48.

α-(Benzotriazol-1-yl)acetophenone (**4.13**) (0.12 g, 0.5 mmol, 6%) was obtained (R_f 0.30) as the second fraction. Starting material **4.16** was recovered (0.06 g, 0.2 mmol, 3%) as the third fraction (R_f 0.10).

Method B. A mixture of benzotriazole (1.19 g, 10.0 mmol), sodium methylate (0.54 g, 10.0 mmol) and ethanol (20 ml) was stirred under nitrogen for 1 h and desyl chloride (**4.21**) (2.31 g, 10.0 mmol) added. The mixture was heated at 70 °C for 14 h. After cooling, the solution was passed through a filter paper and the solvent evaporated to give a yellow solid (2.98 g), which was subjected to column chromatography (hexane-CH_2Cl_2 1:1) to give **4.20** (1.09 g, 3.48 mmol, 35%), identical with the sample obtained by method A.

CHAPTER V
LITHIATION OF
1-ALKYL AND 2-ALKYLBENZOTRIAZOLES

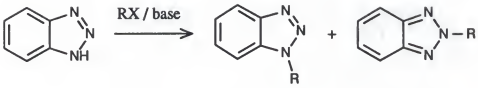
5.1 Foreword

The simplest alkylbenzotriazoles, 1- and 2-methylbenzotriazoles were reported as early as 1914 [14CB672]. However, no lithiation of either 1-alkylbenzotriazoles or 2-alkylbenzotriazoles has been reported. We report here some initial results of lithiation for both 1-alkylbenzotriazoles and 2-alkylbenzotriazoles.

5.2 Lithiation of 1-Alkylbenzotriazoles

5.2.1 Introduction

The 1-substituted alkylbenzotriazoles and their 4-nitro derivatives are of wide interest due to their biological activities as herbicides [78JAP(K)78121762, 77BEP-853179, 78FES924, 80USP4240822, 78USP4086242, 78FES901] insecticides [77BEP-853179], and acaricides [78JAP(K)78121762]. Unfortunately, direct alkylation of benzotriazole leads to a mixture of its 1-alkyl (**5.1**) and 2-alkyl (**5.2**) derivatives (Scheme 5.1) [54JA1847, 35LA113, 38CB596, 56JCS1076, 75JCS(P2)1695, 80USP-4240822, 78FES901, 79HCA2129, 77BCJ1510, 80MI107, 79TL4709, 85H2895, 83BCJ280, 79MI787, 84TL1957]. In the case of the products with a small alkyl group (methyl, ethyl, propyl) fractional vacuum distillation provides satisfactory separation of the isomers [54JA1847, 35LA113, 38B596]. Separation of 1- and 2-benzotriazoles with



5.1 **5.2**

Scheme 5.1

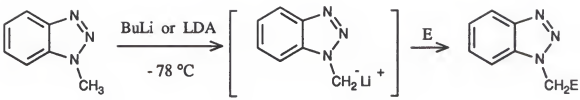
larger alkyl groups requires extraction with an organic solvent of the less basic Bt(2) isomers from their solutions in hydrochloric acid [80USP4240822, 79HCA2129]. 1-Alkylbenzotriazoles with bulky alkyl groups are difficult to separate from their Bt(2) isomers and have usually been prepared selectively in a multistep sequence via cyclization of appropriately monosubstituted *o*-phenylenediamines with nitrous acid [80USP4240822, 77BEP853179, 57JCS4559].

An *N*-benzotriazolyl group is known to activate an adjacent C-H towards proton loss. Thus compounds of type Bt-CH_2-X can be lithiated at the CH_2 carbon where X is phenyl [90MI21], silyl [90MI21], SR [91HCA1931], OR [91JCS(P1)329] or *N*-heterocycle [89HC829, 91S666]. Deprotonations of such compounds followed by reactions with electrophiles and subsequent transformations have led to several useful synthetic methods.

We now disclose that such lithiations also occur in the absence of additional activation in 1-alkylbenzotriazoles (**5.1**), and subsequent treatment with electrophiles leads to a variety of 1-substituted benzotriazoles (**5.4a-5.4i**).

5.2.2 Results and Discussion

Stirring one equivalent of butyllithium with 1-methylbenzotriazole (**5.1**) in tetrahydrofuran (THF) at -78 °C under argon for 30 min. formed 1-(lithiomethyl)-



5.1a **5.3** **5.4a-5.4i**

(see Table 5.1 for E)

Scheme 5.2

benzotriazole **5.2** as demonstrated by trapping the anion **5.2** with various electrophiles (Scheme 5.2). However, **5.3** is of low stability, when its solution was allowed to warm up to -50 °C and kept for 1 h, apart from **5.1a** a complex mixture was recovered indicating a partial decomposition of **5.3** at this temperature. Intermediate **5.3** was also generated by lithium diisopropylamide (LDA) and trapped by deuterium oxide as 1-deuteriomethylbenzotriazole (**5.4a**). Reaction of **5.3** with alkyl bromides or iodides gave the corresponding 1-alkylbenzotriazoles (**5.4b-5.4d**) [35LA113, 78FES901, 87-JCS(P1)781] in good yields (Scheme 5.2, Table 5.1). With aromatic aldehydes and ketones, high yields of the corresponding alcohols (**5.4f-5.4g**) were obtained. Anion **5.3** reacted with acrolein regiospecifically to give the corresponding alcohol as the 1,2-addition product. Use of ethyl benzoate or carbon dioxide afforded α-(benzotriazol-1-yl)acetophenone (**5.4h**) [90AJC133] or benzotriazol-1-ylacetic acid (**5.4i**) [35LA113] respectively in moderate yields. The yields were not optimized and in most cases, 1-methylbenzotriazole was also recovered. All the compounds obtained were fully characterized by their ^{1}H and ^{13}C NMR (Tables 5.2-5.3), which confirmed their assigned structures.

We found that the reaction conditions used for 1-methylbenzotriazole (**5.1a**) could not be directly applied for the lithiation of 1-ethylbenzotriazole (**5.1b**). When

Table 5.1 Characterization for α-Substituted 1-Methylbenzotriazoles **5.4a-5.4i**.

Cmpd	Electrophile	Yield (%)	M.P. (°C) or B.P. (°C/mm)	Formula	Analysis					
					Calcd.			Found		
					C	H	N	C	H	N
a	D_2O	60		$C_7H_6DN_3$	a					
b	MeI	80	100/0.03[b]	$C_8H_9N_3$	[35LA113]					
c	BuI	53	oil	$C_{11}H_{15}N_3$	[78FES901], c					
d	$PhCH_2Br$	30	oil	$C_{14}H_{13}N_3$	[87JCS(P1)781], d					
e	CH_2=CHCHO	57	oil	$C_{10}H_{11}N_3O$	e					
f	PhCHO	95	147-148	$C_{14}H_{13}N_3O$	70.60	5.57	17.43	70.28	5.48	17.56
g	PhCOPh	70	127-129	$C_{20}H_{17}N_3O$	75.93	5.51	13.28	76.17	5.43	13.32
h	PhCOOEt	54	107-110	$C_{14}H_{11}N_3O$	66.66[f]	4.79[f]	22.21[f]	66.27	4.71	22.32
i	CO_2	54	212-213[g]	$C_8H_7N_3O_2$	[35LA113]					

a) Compound **5.4a** was not separated from its non-deuteriated isomer **5.1a**; HR MS Calcd.: 134.0703. Found: 134.0708.
b) Lit. b.p. 149.5 °C/12 mm.
c) HR MS Calcd.: 189.1266. Found: 189.1265.
d) HR MS Calcd.: 223.111. Found: 223.111.
e) HR MS Calcd.: 189.0902. Found: 189.0894.
f) Data for the oxime of **5.4h**.
g) Lit. m.p. 212-213 °C.

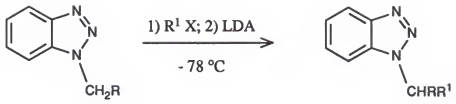
Table 5.2 ^{1}H NMR Data of α-Subtituted 1-Methylbenzotriazoles **5.4a** and **5.4e-5.4h**.

Cmpd	Benzotriazole Moiety				H-α	H-Others
	H-4	H-5	H-6	H-7		
a	8.00[a]	7.30-7.50[a]	7.30-7.50[a]	7.30-7.50[a]	4.24 (s)	-
e	7.83	7.28	7.44	7.61	4.58 (dd 7.9 14.0)	3.60 (bs 1H OH), 4.82 (m 1H CHO),
	(d 8.4)	(dd 6.9 8.4)	(dd 6.9 8.4)	(d 8.4)	4.72 (dd 3.5 14.1)	5.25 (d 10.5 1H), 5.42 (d 17.2 1H),
						5.97 (ddd 5.6 10.5 16.3 1H)
f	7.85	7.25-7.55[a]	7.25-7.55[a]	7.25-7.55[a]	4.72 (dd 8.3 14.2)	3.62 (bs 1H OH), 5.37 (dd 3.9 8.5 1H
	(d 8.4)	-	-	-	4.81 (dd 3.9 14.2)	PhCHO), 7.25-7.55 (a)
g	7.91	7.20-7.50[a]	7.20-7.50[a]	7.20-7.50[a]	5.29 (s)	4.44 (bs 1H OH), 7.20-7.50 (a)
	(d 8.0)	-	-	-		
h	8.05	7.30-7.50[a]	7.30-7.50[a]	7.30-7.50[a]	6.08 (s)	7.51 (dd 7.3 8.0 2H), 7.64 (t 7.4 1H),
	(d 8.4)	-	-	-		8.02 (d 7.1 2H)

a) Overlapping signals do not allow definition of multiplicity.

Table 5.3 ^{13}C NMR Data of α-Substituted 1-Methylbenzotriazoles **5.4a** and **5.4e-5.4h**.

Cmpd	Benzotriazole Moiety						C-α	C-Others
	C-4	C-5	C-6	C-7	C-3a	C-7a		
a	119.4	123.5	127.0	108.9	145.6	133.2	33.7 (t 21.5)	-
e	119.4	123.9	127.3	110.1	145.3	133.7	53.6	71.8, 117.4, 136.5
f	119.5	123.9	127.3	109.9	145.4	133.7	55.5	73.3, 125.9 (2C), 128.4, 128.7 (2C), 140.4
g	119.7	123.8	127.4	109.7	145.0	134.0	57.3	78.5, 126.2 (4C), 127.7 (2C), 128.3 (4C), 143.4 (2C)
h	119.9	123.9	127.7	109.5	145.9	133.7	53.7	128.1 (2C), 129.0 (2C), 133.9, 134.4, 190.3



5.1b R = Me

5.1c R = Et

R^1 X = MeI, EtBr, PrI

	R	R^1
5.5a	Me	Me
5.5b	Me	Et
5.5c	Me	Pr
5.5d	Et	Et

Scheme 5.3

5.1b was treated at -78 °C with butyllithium followed, after either 30 min. or 2 h at this temperature, by addition of methyl iodide, complex mixtures were obtained. Treatment of **5.1b** with butyllithium at -78 °C for 2 h followed by deuterium oxide also resulted in a complex mixture. Reaction of **5.1b** with LDA at -78 °C for 2 h followed by ethyl iodide gave only trace amounts of expected 1-(1-methylpropyl)benzotriazole (**5.5b**). All these experiments indicated that in comparison with 1-methylbenzotriazole, the anion derived from 1-ethylbenzotriazole was less stable and underwent spontaneous decomposition even at -78 °C. The α-carbanion of a 1-substituted benzotriazole is known to decompose to an imine and nitrogen gas [91CB1431].

In recognition of this reason, successful alkylations were achieved in moderate to good yields by direct treatment of a mixture of an 2-alkylbenzotriazole and an alkyl halide at -78 °C (Scheme 5.3, Table 5.4). 2-alkylbenzotriazoles were recovered (9%-61%) and the yields were not optimized. Thus, treatment of a mixture of 1-ethylbenzotriazole (**5.1b**) and methyl iodide (2.5 equiv.) with LDA (2.5 equvi.) at -78 °C gave 1-(1-methylethyl)benzotriazole (**5.5a**) in 15% yield with 61% recovery of **5.1b**.

Treatment of a mixture of **5.1b** and ethyl bromide at -78 °C for 3 h gave 1-(1-methylpropyl)benzotriazole (**5.5b**) in 45% yield with 29% recovery of **5.1b**, and the yield **5.5b** was increased to 72% (with 9% recovery of **5.1b**) when reaction time was increased to 15 h indicating the deproronation of **5.1b** by LDA was reversable. The low yield in the case of methyl iodide seems to reflect the relatively high reactivity of methyl iodide towards LDA in comparison with that of ethyl bromide. Similarly, reaction of **5.1b** with 1-iodopropane afforded 1-(1-methylbutyl)benzotriazole (**5.5c**) [78FES901] in 44% yield (with 34% recovery of **5.1b**). Compounds **5.5a-5.5d** were identified by HR MS (Table 5.4) and ^{1}H NMR (Table 5.5) and ^{13}C NMR (Table 5.6).

Table 5.4 Characterization for α-Substituted 1-Alkylbenzotriazoles **5.5a-5.5d**.

Cmpd	Reagents	Yield (%)	B.P. (°C/mm)	Formula	HR MS Calcd. Found	Reference
a	Bt^{1}Et + MeI	15	oil	$C_9H_{11}N_3$	162.1031[a] 162.1036[a]	89JHC1579
b	Bt^{1}Et + EtBr	72	104-7/0.20[b]	$C_{10}H_{13}N_3$	175.1109 175.1105	77JOM169
c	Bt^{1}Et + PrI	44	103-4/0.05[c]	$C_{11}H_{15}N_3$	189.1266 189.1276	78FSE901
d	Bt^{1}Pr + EtBr	40	oil	$C_{11}H_{15}N_3$	189.1266 189.1270	80USP4240822

a) $(M+1)^+$.
b) Lit. b.p. 156 °C/13 mm.
c) Lit. b.p. 98-104 °C/0.05-0.10 mm.

Propylbenzotriazole **5.1c** underwent lithiation and alkylation similarly to 1-ethylbenzotriazole (**5.1b**). Thus, treatment of 1-propylbenzotriazole and bromoethane with LDA gave 1-(1-ethylpropyl)benzotriazole (**5.5d**) in 40% yield (with 32% recovery of **5.1c**). The published synthetic method for this compound [80USP4240822] involves

Table 5.5 ^{1}H NMR Data of α-Substituted 1-Alkylbenzotriazoles **5.5a-5.5d.**

Cmpd	Benzotriazole Moiety				H-α	H-Others
	H-4	H-5	H-6	H-7		
a	8.05	7.35	7.43-7.60	7.43-7.60	5.08	1.73 (d 6.8 6H)
	(d 8.4)	(m)	(m)	(m)	(hep 6.8)	
b	8.06	7.34	7.45	7.56	4.83	0.82 (t 7.4 3H), 1.70 (d 6.8 3H),
	(d 8.3)	(m)	(m)	(d 8.3)	(m)	2.04 (m 1H), 2.18 (m 1H)
c	8.06	7.34	7.45	7.56	4.94	0.87 (t 7.3 1H), 1.14 (m 1H),
	(dt 8.3 1.7)	(ddd,	(ddd,	(dt 8.3 1.0)	(m)	1.27 (m 1H), 1.70 (d 6.8 3H),
		1.1 6.8 8.2)	1.0 6.8 7.9)			1.95 (m 1H), 2.20 (m 1H)
d	8.07	7.35	7.47	7.55	4.58	0.77 (t 7.4 6H), 2.05 (m 2H),
	(dt 8.3 1.0)	(m)	(m)	(dt 8.3 1.0)	(m)	2.20 (m 2H)

Table 5.6 ^{13}C NMR Data of α-Substituted 1-Alkylbenzotriazoles **5.5a-5.5d**.

Cmpd	Benzotriazole Moiety						C-α	C-Others
	C-4	C-5	C-6	C-7	C-3a	C-7a		
a	118.8	123.6	126.6	109.5	146.0	131.9	51.4	22.0 (2C)
b	119.7	123.4	126.6	109.4	145.9	132.3	57.3	10.5, 20.1, 29.2
c	119.8	123.5	126.7	109.5	145.9	132.3	55.6	13.4, 19.3, 20.5, 38.2
d	119.8	123.5	126.7	109.6	145.9	133.0	63.9	10.6 (2C), 27.7 (2C)

condensation of 2-chloronitrobenzene with 1-ethylpropylamine, reduction of the nitro group and diazotization of the 2-(1-ethylpropyl)aminoaniline obtained with sodium nitrite in acetic acid.

Treatment of a mixture of 1-ethylbenzotriazole (**5.1b**) and benzophenone (or benzaldehyde) with LDA did not give the expected alcohol but both starting materials were recovered. In the case of benzaldehyde, benzyl alcohol was also obtained, which probably formed from benzaldehyde in a Cannizaro reaction during the basic work-up.

In conclusion, lithiation of readily available 1-methylbenzotriazole followed by reactions with alkyl halides or other electrophiles provides a simple and versatile method for the preparation of 1-substituted benzotriazoles, with larger primary alkyl or other more complex groups. Treatment of a mixture of 1-(n-alkyl)benzotriazoles and an alkyl halide with LDA provides a versatile one step method for the preparation of benzotriazoles selectively substituted at *N*-1 with secondary alkyl groups.

5.2.3 Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus or with a hot-stage microscope and were not corrected. Proton and carbon NMR spectra were obtained on a Varian VXR-300 instrument in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) as the internal standard. Coupling constants (J) were given in Hz. High resolution mass spectra were recorded at 70 ev with an A.E.I. MS-30 mass spectrometer with a Kratos DS-55 data system. Elemental analyses were performed under the supervision of Dr. David H. Powell. Diethyl ether and tetrahydrofuran (THF) were dried by refluxing with sodium and benzophenone and distilled immediately prior to use. Column chromatography was performed on MCB silica gel (230-400).

General procedure: lithiation of 1-methylbenzotriazole and preparation of **5.4a-5.4i**. To a stirred solution of 1-methylbenzotriazole (**5.1a**) (1.50 g, 11.27 mmol) in dry THF (40 ml) under argon at -78 °C was added dropwise 2.5 M BuLi (5.0 ml, 12.39 mmol) in hexane and the colorless solution became dark red immediately. After stirring for 4 h, the proper electrophile (11.27 mmol) (or solutions in THF for solids) was added dropwise (excess CO_2 was introduced directly) and the mixture was allowed to warm up to 25 °C overnight. The reaction mixture was poured to water (50 ml), neutralized with acetic acid (or acidified to pH 1 with HCl for **5.4i**), extracted with diethyl ether or ethyl acetate (3 x 50 ml) and dried ($MgSO_4$). After removal of the drying agent and solvents, the crude product was obtained, which was purified properly and characterized (Tables 5.1-5.3).

General procedure: α-alkylation of 1-alkylbenzotriazoles and preparation of **5.5a-5.5d**. To a stirred solution of 1-ethylbenzotrizole (**5.1b**) (1.47 g, 10.0 mmol) and a proper electrophile (25.0 mmol) in THF (30 ml) at -78 °C under nitrogen was added 1.5 M LDA (16.7 ml, 25.0 mmol) dropwise. The mixture was stirred for 3 to 46 h at -78 °C and qhenched with 20% ammonium chloride (10 ml). The mixture was extracted with diethyl ether (100 ml), washed with water (3 x 100 ml), and dried ($MgSO_4$). After removal of the drying reagent and solvent, product **5.5** was obtained, which was characterized properly (Tables 5.4-5.6).

5.3 Lithiation of 2-Alkylbenzotriazoles

5.3.1 Introduction

As documented in section 5.2.1, direct alkylation of benzotriazole produces a mixture of 1- (**5.1**) and 2-alkylbenzotriazoles (**5.2**) in a ratio depending to some extent on the nature of the alkylating agent and the reaction conditions (Scheme 5.1, section

5.2.1). In our development of the chemistry of *N*-substituted benzotriazoles [91T2683] we have become accustomed to identical or very similar chemical behavior for benzotriazol-1-yl {Bt(1)} and benzotriazol-2-yl {Bt(2)} derivatives. Indeed, in many cases these two isomers exist in equilibrium with each other. Thus, *N*-(α-amino-alkyl)benzotriazoles existing in solution at room temperature as pairs of rapidly inter-converting Bt(1) and Bt(2) tautomers [75JCS(P1)1181, 87JCS(P1)2673, 90CJC446]. Even pure hydrocarbon substitutes show analogous behavior: at elevated temperature (175-250 °C) 1-(diphenylmethyl) and 1-(triphenylmethyl)benzotriazoles equilibrate with their 2-substituted analogs [90JCS(P2)2059].

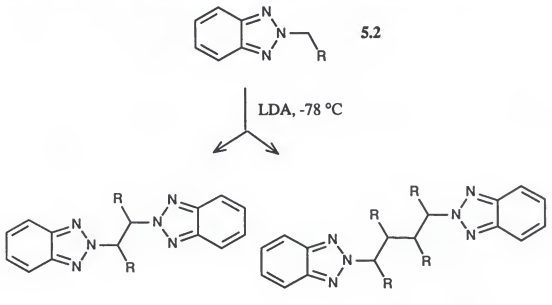
Therefore, it was initially quite surprising to find that lithiation of the 2-alkylbenzotriazoles (**5.2**) differs from that of 1-alkylbenzotriazoles (**5.1**). This section describes the results of some initial studies of the lithiation of 2-alkylbenzotriazoles, and rationalization for the astonishingly different behavior.

5.3.2 Results and Discussion

5.3.2.1 α,α-Coupling of 2-alkylbenzotriazoles

As reported in section 5.2.2, 1-deuteriomethylbenzotriazole (**5.3a**) was obtained from 1-methylbenzotriazole (**5.1**) after lithiation with LDA or butyllithium at -78 °C and subsequent treatment with deuterium oxide. However, when 2-methylbenzotriazole (**5.2a**) was treated with butyllithium at -78 °C for 40 min. followed by deuterium oxide, a complex mixture was obtained; no **5.2a** or its α-deuteriated derivative was detected by NMR, but 1,2-di(benzotriazol-2-yl)ethane (**5.7a**) was identified as the main product. Direct treatment of **5.2a** with LDA alone at -78 °C for 6 h afforded compound **5.7a** in 84% yield (Scheme 5.4), which was fully characterized by analysis and ^{1}H and ^{13}C NMR (Tables 5.7-5.9). Analogous coupling products **5.7b**, **5.7c** and **5.7d** were also

obtained from the corresponding 2-alkylbenzotriazoles (**5.2b**-**5.2d**) (dimers **5.7c** and **5.7d** were obtained from **5.2c** and **5.2d** prepared in situ by alkylation of 2-methyl-benzotriazole (**5.2a**) with ethyl iodide and benzyl bromide respectively, see section 5.3.2.3 for details) (Scheme 5.4). A characteristic feature of this reaction is the formation of only one diastereomer (either meso or dl, to be determined) of **5.7**.



5.7a **5.7b** **5.7c** **5.7d** **5.8b**, R = Me

R = H Me Et CH_2Ph

Scheme 5.4

Some difficulties were encountered during the purification of the coupling product (**5.7b**) of 2-ethylbenzotriazole. The ^1H NMR spectrum of **5.7b** showed a multiplet at δ 5.75 ppm for the methine and a doublet at δ 1.88 ppm for the methyl, and the ^{13}C NMR spectrum showed two aliphatic peaks at δ 66.3 ppm for the methine and δ 16.9 ppm for the methyl. However, the ^1H NMR spectrum of the 'purified' product showed two additional multiplets at δ 4.94 and 2.71 ppm with the same integrals and two additional doublets at δ 1.77 and 0.60 ppm both with three times of integrals

Table 5.7 Characterization of Dimers **5.7a-5.7d.**

Cmpd.	Yield	M.P. (°C)	Formula	Analysis Calcd. (Found)		
				C	H	N
a	84	150-153	$C_{14}H_{12}N_6$	63.63	4.58	31.80
				(63.26)	(4.61)	(32.08)
b	46	115-118	$C_{16}H_{16}N_6$	65.74	5.52	28.75
				(65.44)	(5.54)	(28.46)
c	74	204-206	$C_{18}H_{20}N_6$	67.48	6.29	26.23
				(67.20)	(6.31)	(26.60)
d	18	177-179	$C_{28}H_{24}N_6$	75.65	5.44	18.90
				(75.83)	(5.42)	(18.67)

compared to that of the two additional doublets, plus additional signals from benzotriazole moiety, which were shifted downfield compared to that of **5.7b**. The ^{13}C NMR spectrum showed four additional aliphatic peaks at δ 66.8, 39.8, 19.4 and 10.0 ppm. Compound **5.7b** has three stereoisomers: one meso and two dl isomers. However, the two dl isomers should give the same ^{1}H and ^{13}C NMR spectra if no chiral agents are used to obtain the spectra and a mixture of the three stereoisomers mentioned above would give no more than two sets of NMR signals. Clearly, the 'purified' product must contain a new compound. This new product was finally separated from **5.7b** as **5.8b** (Scheme 5.4) by careful column chromatography in 19% yield and characterized by analysis and NMR (Tables 5.7-5.9). Compound **5.8b** is evidently formed from four molecules of **5.2a** with the elimination of two molecules of benzotriazole. Surprisingly, despite of four asymmetric centers in the molecule, only one stereoisomer of **5.8b** was obtained. *X*-Ray structure determination of **5.8b** is in progress.

Table 5.8 ^{1}H NMR Data of Dimers **5.7a-5.7d.**

Cmpd.	Benzotriazole Moiety		H-α	H-Others
	H-4 H-7	H-5 H-6		
a	7.81	7.36	5.47	-
	(m 4H)	(m 4H)	(s 4H)	
b	7.74	7.30	5.75	1.88 (d 6.3 6H)
	(m 4H)	(m 4H)	(m 2H)	
c	7.72	7.26	5.55	0.75 (t 7.3 6H),
	(m 4H)	(m 4H)	(m 2H)	2.61 (m 2H), 2.42 (m 2H)
d	7.66	7.23	5.81	3.79 (m 4H),
	(m 4H)	(m 4H)	(m 2H)	7.11-7.18 (m 10H)

Table 5.9 ^{13}C NMR Data of Dimers **5.7a-5.7d.**

Cmpd.	Benzotriazole Moiety			C-α	C-Others
	C-4, 7	C-5, 6	C-3a, 7a		
a	118.1	126.6	144.5	55.1	-
b	118.1	126.2	144.0	66.3	16.9
c	118.1	126.1	143.8	72.1	10.1, 24.9
d	118.0	126.2	143.8	70.9	37.1, 126.8, 128.4, 128.8, 136.1

Table 5.10 Characterization of Derivatives **5.8b**, **5.9b**, and **5.22**.

Cmpd.	Yield	M.P. (°C)	Formula	Analysis Calcd. (Found)		
				C	H	N
5.8b	19	170-171	$C_{20}H_{24}N_6$	68.94	6.94	24.12
				(68.91)	(6.91)	(24.30)
5.9b	18	180-182	$C_{22}H_{28}N_6$	a		
5.22	95	159-161	$C_{20}H_{17}N_3$	76.17	5.43	13.32
				(76.31)	(5.35)	(13.36)

a) HR MS Calcd. for $(M+1)^+$: 377.2454. Found: 377.2437.

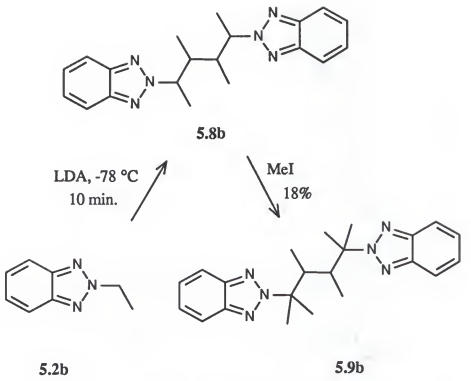
Table 5.11 ^{1}H NMR Data of Derivatives **5.8b**, **5.9b** and **5.22**.

Cmpd.	Benzotriazole Moiety		H-α	H-Others
	H-4 H-7	H-5 H-6		
5.8b	7.89	7.40	4.94	0.60 (d 6.6 6H), 1.77 (d 6.7 6H),
	(m 4H)	(m 4H)	(m 2H)	2.71 (m 2H)
5.9b	7.85	7.33	-	0.51 (d 7.1 6H), 1.67 (s 6H),
	(m 4H)	(m 4H)		1.68 (s 6H), 2.62 (q 7.1 2H)
5.22	7.78	7.32	5.42	6.09 (s 1H OH), 7.18 (t 7.3 2H),
	(m 2H)	(m 2H)	(s 2H)	7.27 (dd 6.3 7.8 4H), 7.54 (d 7.3 4H)

Table 5.12 ^{13}C NMR Data of Derivatives **5.8b**, **5.9b** and **5.22**.

Cmpd.	Benzotriazole Moiety			C-α	C-Others
	C-4, 7	C-5, 6	C-3a, 7a		
5.8b	118.0	126.2	143.9	66.8	10.0, 19.4, 39.8
5.9b	118.0	125.9	143.5	70.9	11.0, 25.1, 25.6, 41.9
5.22	117.9	126.7	143.6	64.0	78.1, 126.1, 127.5, 128.3, 143.3

Some experiments were carried out in order to understand the reaction mechanism. A solution of 2-ethylbenzotriazole (**5.2b**) in THF were treated at -78 °C with 1.1 equivalents of LDA and quenched with 20% ammonium chloride after 1 h. A second solution of **5.2b** in THF was treated identically except that it was allowed to stand at -78 °C for 51 h. Similar work-up of both experiments gave crude product mixtures in which the yields of individual compounds were estimated on the basis of integrals in the ^1H NMR. The amounts of **5.8b** (20%) and **5.2b** (4%) recovered were constant in these experiments, but the amount of **5.7b** decreased from 46% after 1 h to 6% after 51 h (while the amount of benzotriazole, although the data here may not be accurate since it is soluble in water and may be lost during work up, increased from 9% to 29%). Another product **5.9b** (characterized in Tables 5.10-5.12), which is the dimethylated derivative of **5.8b** at the two α-positions of both Bt(2) moieties, was obtained in 18% yield by treatment of 2-ethylbenzotriazole with LDA at -78 °C for 10 min. followed by addition of methyl iodide (Scheme 5.5).

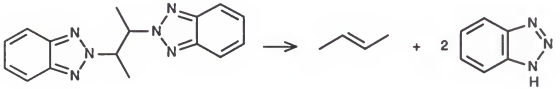


Scheme 5.5

The independence of the yield of compound **5.8b** (or its derive **5.9b**) on time suggests the quick formation of **5.8b** and its stability under the reaction conditions employed; while the decrease of the amounts of **5.7b** and the increase of that of benzotriazole with time indicates decomposition of **5.7b** to benzotriazole and other compound(s), which may be volatile or easily soluble in water and therefore were not detected.

Some related work carried out in this laboratory found that when derivatives **5.2** bearing larger alkyl groups were treated with LDA and allowed to stand at -78 °C for 10-20 h, symmetrical alkenes **(5.18)** were obtained in high yields with strong predominance of the *E* isomers. Thus, *E*-5-decene and *E*-6-dodecene were obtained from 2-pentylbenzotriazole and 2-hexylbenzotriazole in 85% and 75% yields respectively as the only isomers, and 10-eicosene was obtained from 2-decyl-

benzotriazole in 85% yield as a mixture of *E* and *Z* isomers (*E*:*Z* = 2:3). Therefore, we conclude that compound **5.7b** decomposed slowly at -78 °C to 2-butene and benzotriazole (Scheme 5.6).

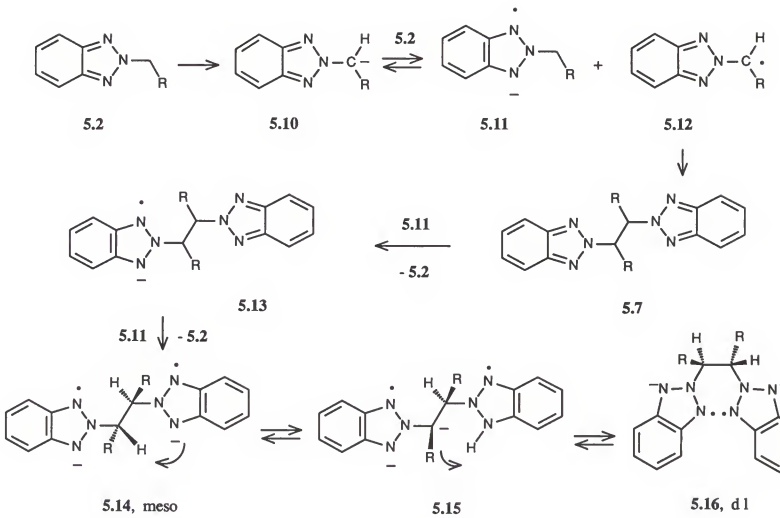


5.7b

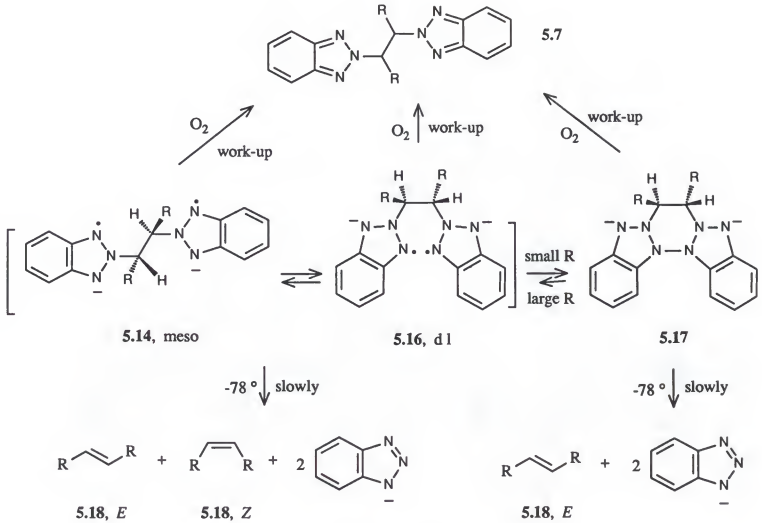
Scheme 5.6

In 1988, Pedersen and Lund published a paper on electrochemical reductions of some 2-alkylbenzotriazoles in which they were reduced to relatively stable radical anions [88ACS(B)319].

These experimental facts are consistent with the following mechanisms (Scheme 5.7). Alkylbenzotriazole **5.2** is deprotonated at its α-carbon by LDA generating anion **5.10**, which can be oxidized quickly by **5.2** to radical **5.12**, with simultaneous reduction of **5.2** to radical anion **5.11**. Radical **5.12** combines immediately to dimer **5.7**, which takes up an electron from the relatively stable radical anions **5.11** (or from anion **5.10** converting it to radical **5.12**) oxidizing it back to starting material **5.2** and converting itself to radical anion **5.13**. Radical anion **5.13** picks up another electron becoming diradical dianion **5.14** or **5.16**. There is a fast equilibrium between the meso (**5.14**) and dl (**5.16**) isomers via proton exchange through intermediate **5.15**. The dl isomers **5.16** cyclize spontaneously to a fused 6-membered ring dianion intermediate (**5.17**) with the two alkyl groups trans to each other. Dianion

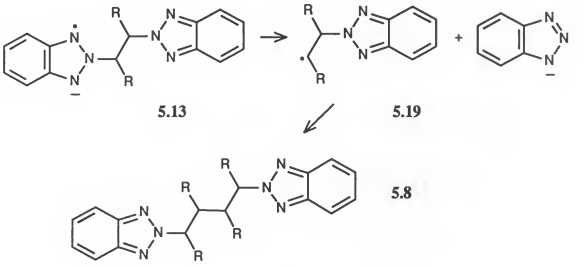


Scheme 5.7



Scheme 5.7 (continued)

(**5.17**) is relatively stable at -78 °C, however, it is oxidized to dimer **5.7** upon work-up, and may eliminate two benzotriazole anions slowly at -78 °C affording *E*-alkene (**5.18**, *E*). When the alkyl group is large (e.g., R is decyl), formation of **5.17** becomes difficult because of steric hindrance and both *E*- and *Z*-alkenes (**5.18**) are formed from **5.14** and **5.16** directly.



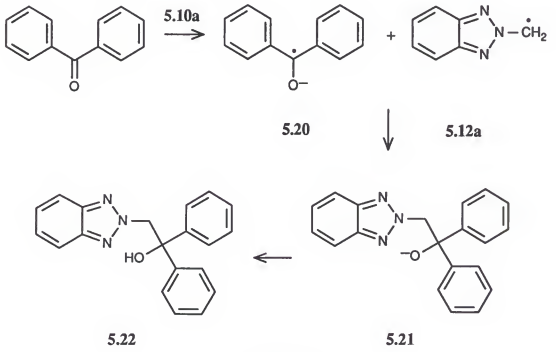
Scheme 5.8

Radical anion **5.13** may compete with the process of accepting a second electron giving **5.14** or **5.16** by eliminating a benzotriazole anion and forming radical **5.19** when R is an alkyl group, which can stabilize the radical. Combination of **5.19** forms derivative **5.8** (Scheme 5.8).

It is also possible that anion **5.10** takes the role of **5.2** as an electron carrier by picking up an electron from another molecule of **5.10** becoming a radical dianion (the α-deprotonation product of **5.11**) and delivers it to either **5.7** or **5.13**.

5.3.2.2 Reactions with aldehydes and ketones

Treatment of a mixture of 2-methylbenzotriazole (**5.2a**) and benzophenone with LDA at -78 °C gave the corresponding carbonyl addition product **5.22** in nearly quantitative yield; whereas under the same conditions benzaldehyde or β,β-diphenyl-acrolein did not give the expected alcohols, only dimer **5.7a** was obtained as the main product with recovery of the aldehyde. We believe that benzophenone is a much stronger electron acceptor and oxidized anion **5.10a** from **5.2a** exclusively to radical **5.12a** while converting itself to radical anion **5.20**. Combination of radicals **5.12a** and **5.20** afforded anion **5.21**, which gave alcohol **5.22** after work-up. Whereas benzaldehyde or β,β-diphenylacrolein is a poorer electron acceptor than **5.2a** and thus did not react similarly. Direct nucleophilic addition of anion **5.10a** to the carbonyl

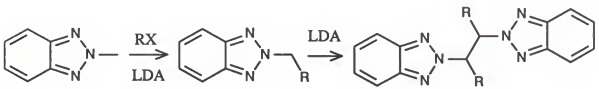


Scheme 5.9

group of either benzophenone or benzaldehyde is a relatively slow process and can not compete with the radical processes described above (Scheme 5.9).

5.3.2.3 Alkylation with alkyl halides

When a mixture of 2-methylbenzotriazole (**5.2a**) and ethyl iodide was treated with two equivalents of LDA at -78 °C, dimer **5.7c** was obtained in 74% yield (Scheme 5.10). Use of benzyl bromide as electrophile afforded the α-benzylated derivative **5.2d** in addition to dimer **5.7d**. We believe the α-alkylation products (**5.2c** and **5.2d**) were obtained first, which then coupled later to dimers **5.7c** and **5.7d**.

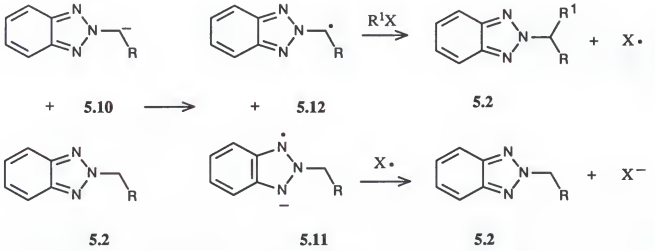


5.2a **5.2c**, R = Et **5.7c**, R = Et

5.2d, R = CH_2Ph **5.7d**, R = CH_2Ph

Scheme 5.10

A radical mechanism is proposed as follows: radical **5.12** derived from anion **5.10** reacts with alkyl halide R^2X giving product **5.2** and the halogen radical ($X^{\cdot}$) generated is reduced to anion X^- while oxidizing **5.11** back to **5.2**. With proper alkyl halide R^2X, radical **5.12** is consumed fast enough keeping its concentration low and thus preventing the competing dimerization of **5.12** to **5.7**. This mechanism is also supported by experiments carried out in this laboratory that treatment of a mixture of 2-propylbenzotriazole and decyl bromide (less reactive) with two equivalents of LDA



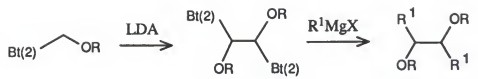
Scheme 5.11

at -78 °C did not yield the corresponding α-alkylated benzotriazole derivative, but dimer **5.7c** was obtained in 65% yield; and that reaction between 2-pentylbenzotriazole and ethyl iodide afforded the corresponding α-alkylated benzotriazole derivative 3-(benzotriazl-2-yl)heptane quantitatively (Scheme 5.11).

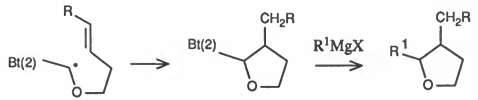
5.3.2.4 Potential applications in organic synthesis

The new radical chemistry of 2-alkylbenzotriazoles may have wide applications in organic synthesis. For example, treatments of 2-alkoxymethylbenzotriazoles **5.23** with LDA may afford dimers **5.24**. Since a benzotriazole group activated by an α-alkoxy substituent can be replaced by a Grignard reagent [89JOC6022], dimers **5.24** are expected to be precursors for synthesis of symmetric α,β-diethers **5.25** (Scheme 5.12). When there is a carbon-carbon double bond in the alkyl chain separated from the oxygen atom by two carbons, the radical intermediate **5.26** may undergo intramolecular cyclization to form the 5-membered ring **5.27**, which may be converted to the α,β-disubstituted tetrahydrofuran **5.28**. Benzotriazol-2-ylmethyl radical may also add to the nitrogen-nitrogen double bond of an azo compound, e.g., azobenzene **5.29**, to give **5.30** type of intermediate which, by treatment with a Grignard reagent, will provide a convenient synthesis of trisubstituted hydrazines **5.31**.

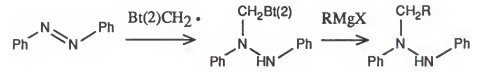
In conclusion, simple treatments of the readily available 2-alkylbenzotriazoles (**5.2**) gave symmetrical α,β-bis(benzotriazol-2-yl)alkanes (**5.7**) selectively in high yields. α-alkylation of 2-alkylbenzotriazoles could be achieved in high yields by reactive alkyl halides. 2-Methylbenzotriazole added quantitatively to benzophenone to give the corresponding tertiary alcohol (**5.22**), but did not react with aldehydes, which is against nucleophilic addition mechanism and supporting the radical mechanism proposed for the formation of the coupled products (**5.7**). The stereoselectivity for the formation of dimers **5.7**, especially for derivative **5.8b** is noteworthy and needs more



5.23 **5.24** **5.25**



5.26 **5.27** **5.28**



5.29 **5.30** **5.31**

Bt(2) = benzotriazol-2-yl

Scheme 5.12

study. The radical chemistry of 2-alkylbenzotriazoles has never been reported and further investigation in this new area is expected to be rewarding, open new areas of study for benzotriazole, and lead to many useful and novel applications of benzotriazole in organic synthesis.

5.3.3 Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus or with a hot-stage microscope and were not corrected. Proton and carbon NMR spectra were obtained on a Varian VXR-300 instrument in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) as the internal standard. Coupling constants (J) were given in Hz. High resolution mass spectra were recorded at 70 ev with an A.E.I. MS-30 mass spectrometer with a Kratos DS-55 data system. Elemental analyses were performed under the supervision of Dr. David H. Powell. Tetrahydrofuran (THF) was dried by refluxing with sodium and benzophenone and distilled immediately prior to use. Silica gel for column chromatography was 230-400 mesh. Column chromatography was performed on MCB silica gel (230-400).

Preparation of **5.7a**. To a stirred solution of **5.2a** (0.72 g, 5.41 mmol) in THF (20 ml) at -78 °C under nitrogen was added 1.5 M LDA in cyclohexane (4.0 ml, 5.96 mmol) dropwise. After stirring at -78 °C for 6 h, the reaction mixture was poured into 50 ml cold 20% ammonium chloride, extracted with diethyl ether (3 x 50 ml), washed with water (3 x 50 ml), and dried ($MgSO_4$). The drying agent was filtered off and solvent evaporated under reduce pressure to give **5.7a** (0.6 g, 2.27 mmol, 84%) as a solid. An analytical sample of **5.7a** was obtained by recrystallization from ethanol/methanol as yellow needles and fully characterized by CHN analysis, ^1H and ^{13}C NMR (Tables 5.7-5.9).

Preparation of **5.7b** and **5.8b**. To a stirred solution of **5.2b** (2.94 g, 20.0 mmol) in THF (40 ml) at -78 °C under nitrogen was added 1.5 M LDA in cyclohexane (14.66 ml, 22.0 mmol) dropwise. After stirring at -78 °C for 1 h, the reaction mixture was poured into 50 ml cold 20% ammonium chloride, extracted with diethyl ether (3 x 50 ml), washed with water (3 x 50 ml), and dried ($MgSO_4$). The drying agent was filtered off and solvent evaporated under reduce pressure to give a mixture of **5.7b** (1.34 g, 4.58 mmol, 46%), **5.8b** (0.33 g, 0.95 mmol, 19%), benzotriazole (9%) and **5.2b** (4%). The sample was subjected to column chromatography to give pure **5.7b** and **5.8b** both as white solids and fully characterized by CHN analysis, ^1H and ^{13}C NMR (Tables 5.7-5.9 and Tables 5.10-5.12).

Preparation of **5.7c**. To a stirred solution of **5.2a** (1.33 g, 10.0 mmol) and ethyl iodide (0.88 ml, 11.0 mmol) in THF (30 ml) at -78 °C under nitrogen was added 1.5 M LDA in cyclohexane (13.3 ml, 20.0 mmol) dropwise. After stirring at -78 °C for 2.5 h, the reaction mixture was poured into 50 ml cold 20% ammonium chloride, extracted with diethyl ether (3 x 50 ml), washed with water (3 x 50 ml), and dried ($MgSO_4$). The drying agent was filtered off and solvent evaporated under reduce pressure to give a residue, which was filtered, washed with diethyl ether (5 ml) and recrystallized from ethanol to give pure **5.7c** as yellow needles (1.19 g, 3.72 mmol, 74%) and fully characterized by CHN analysis, ^1H and ^{13}C NMR (Tables 5.7-5.9).

Preparation of **5.7d** and **5.2d**. To a stirred solution of **5.2a** (1.33 g, 10.0 mmol) and benzyl bromide (1.31 ml, 11.0 mmol) in THF (30 ml) at -78 °C under nitrogen was added 1.5 M LDA in cyclohexane (13.3 ml, 20.0 mmol) dropwise. After stirring at -78 °C for 2 h, the reaction mixture was poured into 50 ml cold 20% ammonium chloride, extracted with diethyl ether (3 x 50 ml), washed with water (3 x 50 ml), and dried ($MgSO_4$). The drying agent was filtered off and solvent evaporated under reduce pressure to give a yellow liquid from which some crystals formed, which was filtered

off (the filtrant saved), and washed with methanol (5 ml) to give **5.7d** (0.40 g, 0.90 mmol, 18%). The sample was recrystallized from ethanol/toluene to give pure **5.7d** as white needles and fully characterized by CHN analysis, ^{1}H and ^{13}C NMR (Tables 5.7-5.9). It was identified by ^{1}H and ^{13}C NMR from the filtrant that **5.2d** was also formed in 20% yield.

Preparation of **5.9b**. To a stirred solution of **5.2b** (1.47 g, 10.0 mmol) in THF (30 ml) at -78 °C under nitrogen was added 1.5 M LDA in cyclohexane (7.33 ml, 11.0 mmol) dropwise. After stirring at -78 °C for 10 min., methyl iodide (0.81 ml, 13.0 mmol) was added dropwise, the dark reaction solution turned orange and precipitates formed quickly. The whole mixture was poured into 50 ml cold 20% ammonium chloride, extracted with diethyl ether (3 x 50 ml), washed with water (3 x 50 ml), and dried ($MgSO_4$). The drying agent was filtered off and solvent evaporated under reduce pressure to give a residue, which was shaked with hexane. The crystals formed were filtered off, washed with hexane, dissolved in diethyl ether (50 ml), washed with 20% NaOH (2 x 20ml), water (2 x 20 ml), and dried ($MgSO_4$). After removal of the drying agent and solvent, pure **5.9b** was obtained (0.17 g, 0.45 mmol, 18%) as white solid and fully characterized by HR MS, ^{1}H and ^{13}C NMR (Tables 5.10-5.12).

Preparation of **5.22**. To a stirred solution of **5.2a** (1.33 g, 10.0 mmol) and benzophenone (1.82 g, 10.0 mmol) in THF (30 ml) at -78 °C under nitrogen was added 1.5 M LDA in cyclohexane (13.3 ml, 20.0 mmol) dropwise. After stirring at -78 °C for 2.5 h, the reaction mixture was poured into 50 ml cold 20% ammonium chloride, extracted with diethyl ether (3 x 50 ml), washed with water (3 x 50 ml), and dried ($MgSO_4$). The drying agent was filtered off and solvent evaporated under reduce pressure to give a solid, which was recrystallized from ethanol to give pure **5.22** as yellow needles and fully characterized by CHN analysis, ^{1}H and ^{13}C NMR (Tables 5.10-5.12).

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Explanation of the Bibliography System

The reference system used here is the same from the book series "Comprehensive Heterocyclic Chemistry," edited by Alan R. Katritzky and Charles W. Rees, Pergamon Press, Oxford, 1984. Throughout this proposal, references are designated a number-letter coding of which the first two numbers denote tens and units of the year of publication, the next one to three letters denote the journal, and the final numbers denote the page. This code appears in the text each time a reference is quoted.

Some commonly used additional notes are given below:

1. The list of references is arranged in order of (a) year, (b) journal in alphabetical order of journal code, (c) part letter or number if relevant, (d) volume number if relevant, (e) page number.
2. In the reference list the code is followed by the complete literature citation in the conventional manner.
3. For journals which are published in separate parts, the part letter or number is given (when necessary) in parentheses immediately after the journal code letters.
4. Journal volume numbers are not included in the code numbers unless more than one volume was published in the year in question, in which case the volume number is included in parentheses immediately after the journal code letters.
5. Patents are assigned appropriate three letter codes.

6. Frequently cited books are assigned codes, but the whole code is now prefixed by the letter "B-."
7. Less common journals and books are given the code "MI" for miscellaneous.
8. Where journals have changed names, the same code is used throughout.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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Kenan Professor of Organic Chemistry

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